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APR 2019 | CUT & PASTE

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Dairy cows often have their horns burned off with hot irons or caustic chemicals. Meet Princess, who was engineered never to grow them.

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Gillette Antiperspirant is partnering with the nonprofit organization Operation Homefront, whose mission is to help build strong, stable, and secure military families so they can thrive in the communities that they have worked so hard to protect. This year, Gillette Antiperspirant will be making a donation to military families in need.

OPERATION HOMEFRONT

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Cymatics: the study of sound and vibration made visible.

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Check it out. Scan below with your camera to learn more (no app needed).

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Tennessee Whiskey, 40% ABV, JACK DANIEL DISTILLERY, Lynchburg, TN

Pitchfork × JACK DANIEL'S

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P 034

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— **Ken Jacobus**, Good Start Packaging CEO

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ELECTRIC WORD

ON THE COVER

PHOTOGRAPH BY CHRISTIE HEMM KLOK

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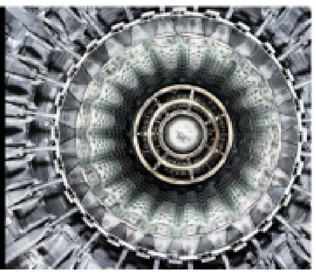

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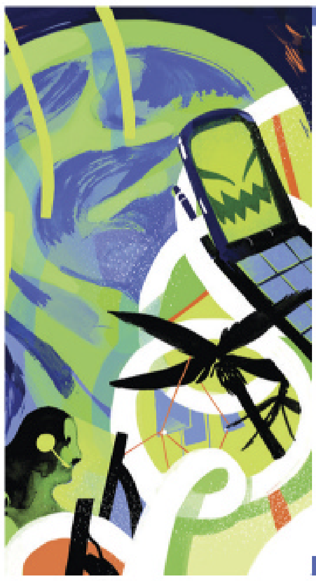

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TOTALLY WIRED

Friends, readers, I have something to confess: A few days ago, I got an offer to Meet a Lovely Russian Woman in my EarthLink email inbox. Yes, there it is: I still have an EarthLink account. I swear I just use it for my Amazingly Cat account. And Facebook.

I was intrigued. Russian women? I'm not even tempted by women, Russian or otherwise. But I was suddenly curious about who else was flooding my EarthLink account, so I started examining the senders in my mushrooming inbox: *Legendz XL, 1ink.com (to be fair, I do need new ink), /*/Male-Enhancements, ***Cannabis***, ///RemoveMoles//. All of them tucked between offers to buy fresh catnip. And Facebook notifications. As I scrolled through, I felt something stir. A rush of warmth, of love, surged through my capillaries. Then came this thought: Thank the lord for AI. My other email inboxes never, ever, ever send me Russian women. Or toenail fungus miracle cures.

You can hate the tech industry all you want—the gargantuan companies that move fast and break everything, the data tracking, the attention hacking, the insipid apps, the skyrocketing housing costs. Plus, I get it: Optimism is so passé.

Whatever. Today, technophobia is eating everything—and it's making us all a little dull. Thank you EarthLink for reawakening me to my own sleepy capacity for technophilia. How? By (apparently) missing the boat on one of the most wonderful, effective, efficient AI-based tools out there. Say it with me: spam filtering.

Spam filtering today is ubiquitous to the point of invisibility. Most of the email coursing through the ether right now is spam; we just don't see it. The offers for Viagra, ads for Russian dates, and phishing attempts almost never reach our eyes.

There are generations alive right now who have no memory of a time when inboxes were jammed with such garbage for days and months. I bet some youngs have no idea what those first two paragraphs I wrote even mean. Male enhancement offers? And that pile of //**//*/*s? (Not to mention: EarthLink? WTF?) Unless you are like old Ripley and hold onto an old email service, you don't know how good we have it now.

Today, some of humankind's most advanced technologists toil to train AI to block penis-pill emails. And while, yes, I'd like those exceptional engineers to turn their impressive talents toward curing cancer, bless them still. Their skills are so good that it is a marvel these businesses—hawking mole removers or printer ink via email—can even survive.

Which is all to say: Allow me to introduce myself, Ripley D. Light. I'll be here every month to share the joy of tech, proudly hiding behind a pseudonym. Because this is about happiness, delight. Also, let's be real: Nobody needs the Twitter hate.

RIPLEY D. LIGHT
@RIPLEYDLIGHT

WE ASKED CONTRIBUTORS:

"WHAT DID YOU LEARN WHILE REPORTING YOUR STORY THAT INTRIGUED YOU THE MOST?"

"From 2015 to 2017, the most active 0.1 percent of Reddit commenters were responsible for 12 percent of the comments on the site." —Robert Peck (page 38)

"That's Princess on the cover, a genetically dehorned cow, but calling her by that name is a little taboo. Scientists aren't supposed to give their research subjects nicknames—they get too attached, potentially distorting their results. And yet, inevitably, they do." —Gregory Barber (page 50)

"In 1972, most cystic fibrosis patients died before the age of 10. Today, people living with CF routinely live into their late thirties, old enough to have children of their own." —Megan Molteni (page 56)

"While it might sometimes feel like robocalls are inescapable, robocalling is actually only a problem in the English-speaking world. Everywhere else, the calls are virtually nonexistent." —Alex W. Palmer (page 84)

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REFLECTING POINT

In our March issue, WIRED senior maverick Kevin Kelly (not pictured above) imagined the coming hegemony of augmented reality, with virtual worlds layered upon the physical; Darren Loucaides explored what happens when techno-utopians actually run a country; and David Dobbs told the stories of hand transplant patients grappling with the procedure's long-term toll. Readers debated whether our vision was clairvoyant or distorted.

> "IN MEDICINE, JUST BECAUSE SOMETHING CAN BE DONE DOESN'T MEAN IT SHOULD BE DONE."

—Robert Weber via mail@WIRED.com

RE: "RIGHT AWAY THEY WERE MINE"

After she lost her hands, an intricate hand transplant technique aimed to make her whole again. Then came the side effects.

"Thank you for this article. In 1971, my left arm was severed by an airplane propeller and then reattached by a surgical team in Los Angeles. I was a medical miracle and also received a lot of press coverage. I had no complications from the long attachment surgery or two other follow-up surgeries. But Western medicine never addressed my trauma or my lifelong neurological pain. For those issues, I looked into alternative therapies and treatments. My healing is my constant companion. There is no way I could have understood that at 15. As I went under for the surgery, all I knew was that I was going to have my arm back. Until Western medicine addresses the emotional toll of such miraculous surgeries, they should only be done with a mental health team in place. I'm just grateful that I had the resources to find people to support me in this unique journey."
—Anne Shelly Baumgarten via mail@WIRED.com

RE: "WELCOME TO MIRRORWORLD"

We are building a 1-to-1 map of almost unimaginable scope. It will become the next great digital platform.

John Moriarty (@john_moriarty) via Twitter:
(1/2) Very interesting, but to be honest I'm surprised by how optimistic the outlook is. What's to say that such a (data-heavy) mirrored reality won't be plagued by the same ethics and trust issues that have come to define the social era?

(2/2) I suppose you answered my question already @kevin2kelly

↳ **Kevin Kelly (@kevin2kelly):**
Over the long term, the future is decided by optimists.

RE: "CAREFUL WHAT YOU WISH FOR"

The inside story of Italy's Five Star Movement and the cyberguru who dreamed it up.

"At last, a piece on the M5S not completely buying into the 'spontaneous protest movement' myth. A must-read for all Italian politics watchers."
—Chiara (@chiara84) via Twitter

PHOTOGRAPH / BETH HOLZER

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The Wired Café @ CES (Consumer Electronics Show) was steps away from the craziness of the Tech West Convention Center and provided an oasis for invited guests and partners to relax and experience the newest innovations that our brand curates. In addition to on-site activations from our sponsors Arrow Electronics, National Geographic and Harley-Davidson that kept our 1000+ guests entertained and engaged, Wired also hosted guided tours of Tech West, providing insights into the trends that are set to shape the upcoming year.

ARROW Valley_of_the_BOOM MOTOR HARLEY-DAVIDSON CYCLES

CLOCK WATCHERS

The beautiful benefits of contemplating doom.

BY VIRGINIA HEFFERNAN

Every year, in late January, a small group of beetle-browed scientists, politicians, and journalists gather at the National Press Club in Washington, DC, to ponder the end of the world. This is a day of solemn kitsch: the unveiling of the Doomsday Clock, the minimalist midcentury dataviz that, since 1947, has been adjusted to dramatize the imminence of global catastrophe. But that's too many syllables. Let's use the shorthand: *doom*. And it's close at hand. The Bulletin of Atomic Scientists, the nonprofit group that maintains the clock, used to set the hands based entirely on the probability of nuclear hellfire. Then in 2007 they added climate change to their calculus and, in 2017, cyberwar. The clock's setting is largely impressionistic. To rough out a relative idea of how safe or imperiled the world is, a committee meets twice a year to weigh signs of peace and climate amelioration—treaties, accords, regulations—against the rumblings of war and environmental disaster.

ILLUSTRATION / ASIA PIETRZYK

On January 24, before a hushed assembly, Jerry Brown, the freewheeling former governor of California, and William Perry, the stern former defense secretary, drew back a heavy black curtain to reveal the iconic clock graphic, now set for 2019—at *two minutes to midnight.* It was like seeing an MRI with bad news. Humankind has been this near to the apocalypse only twice before. The first was in 1953, shortly after the US and Soviet Union started testing hydrogen bombs, and the second was last year, when President Donald Trump was wrapping up his first year of reckless climate denialism and fire-and-fury saber rattling.

> **I get random reminders of my own mortality from WeCroak, an app with notifications that don't mince words.**

The Bulletin's president and CEO is Rachel Bronson, former director of Middle East studies at the Council on Foreign Relations, author of *Thicker Than Oil: America's Uneasy Partnership with Saudi Arabia,* and onetime cochair of Chicago Shakespeare Theater's Producers' Guild. The clock's current setting, she said, reflects the ongoing threats posed by escalating arms races and rising temperatures. Widespread information warfare is amplifying these dangers. The mood in the room was funereal.

That's the Doomsday Clock for you. It'll break your heart. The stark, numberless face shows only the northwest quadrant of an analog clock; the end, by design, is always nigh. But even as I knew the clock had no morning and no afternoon, only dark night, I found it hard to stay clinical about the end. Sorrow almost knocked me out. A rising headache. "Humanity now faces two simultaneous existential threats … the future of civilization in extraordinary danger … frightening reality … too volatile and dangerous … catastrophe of historic proportions." The panelists' words ran together.

To get some focus, I asked Bronson during a break about the graphic, which designer Michael Bierut, who refreshed the image in 2007, calls "the most powerful piece of information design of the 20th century." She told me about Martyl Langsdorf, a painter once known as a social realist prodigy—a Diego Rivera of the American plains. (Langsdorf's yellow-gold 1940 mural *Wheat Workers* shows traditional Kansan harvesters baling hay while ominous smoke from new machines chokes the horizon.) Langsdorf's husband, Alexander Langsdorf, had worked on the Manhattan Project before warning Truman against dropping A-bombs on Japan. At the Bulletin's invitation, Martyl devised the icon for the cover of its first publication, setting her clock at seven minutes to midnight because it "looked good to my eye."

However arbitrary its setting, the clock casts a spell. As I stared at it, the black hands and minute marks came to conjure lakes of fire, ice caps disintegrating like the Twin Towers, five-headed beasts from Revelation or maybe from Chernobyl. But then, as if by a trick of light, the image became brutal and institutional, something you might find in a hospital waiting room, ticking away the time until the grief to end all griefs.

Martyl Langsdorf returned to painting after she designed the clock, moving from allegory to a kind of tranquil abstraction in inky blues and lipstick pinks, and she lived almost a century, through 56 doomsday predictions, and zero actual doomsdays. As a painter married to a physicist, Langsdorf exemplified precisely the civilization the Bulletin says is in peril: fine art and hard science, suffused by a Gandhi-era commitment to peace over war, and to social justice over both anarchy and tyranny.

Milling around, not talking to groovy Jerry Brown (who was mobbed), I tried to separate familiar trepidation about my own death from more expansive fear about the death of the world. I found that the two went hand in hand, and both were abstract, subtly tranquil. They also carried the same imperative: Accept. Idly, I asked one of the Bulletin's publicists if he ever wished he could become a Marvel hero, reverse the polarities, and forestall Armageddon. "Every day," he said. He sounded resigned, but good-humored and alert to irony.

Langsdorf's clock is less an empirical data point than a statement of humanity's self-awareness, proof that we're wise to our own mortality. Awareness of death is notoriously crucial to well-being. For just this reason, I get random reminders of my own mortality from WeCroak, an app with notifications that don't mince words: "Don't forget, you're going to die." Recently it served up E. M. Forster: "Death destroys a man, but the idea of death saves him."

Holding an idea of human extinction doubles as an extended confession of awe at the splendor and devastation we have wrought on Earth. I said there was kitsch here, so forgive me: In recognizing how precious life is—how we are also two minutes from extinction—we live with more vitality. And if consciousness of mortality, beauty, and terror is uniquely human, perhaps the Doomsday Clock *itself* works in furtherance of human civilization.

Civilization. That word kept coming up. Bronson had used it, saying it's threatened by "anomie" and a dangerous departure from the Pax Americana. Conferences on national security and climate science rarely invoke "civilization" by that name; it belongs to the humanities. When scientists in 2019 wonder, broadly, what ends when humans end, they typically define us by our biology. But here the scientists spoke of civilization, not cells. If you listened closely, the panels represented humans as more than an aggressive population of primates dependent on oxygen and water. The phenomenon that sets us apart? We organize ourselves by civilizations. Mayan, Persian, Inca, Etruscan, Egyptian, Greek, Qin, Facebook, all of them.

Jerry Brown, who is known for his Buddhist-Christian explorations, referred in the Q&A to Americans and Russians as "imperfect human beings" with "sins." That was bracing. And Herbert Lin, a senior research scholar for cyber policy and security at Stanford, blew past talk of botnets and troll farms in favor of something grander: "The Enlightenment sought to establish reason as the foundational pillar of civilized discourse. In this conception, logical argument matters, and the truth of a statement is tested by examination of values, assumptions, and facts, not by how many people believe it. Cyber-enabled information warfare threatens to replace these pillars of logic and truth with fantasy and rage."

The Enlightenment! *That* was the specific phase of civilization over whose sickbed we were standing vigil, the historical conceit once regarded as the cradle of all right-thinking: Descartes, Diderot, Hume, Locke. In *Homo Deus*, Yuval Noah Harari argues that "reason" and "liberalism" are Enlightenment fictions ripe to be superseded by artificial intelligence. But never mind Harari. To Lin, as to most of us, it's the Enlightenment that gave us science, modern ethics, the arts, and liberal democracy, and it must not be allowed to perish.

There was relief in this thought. Civilizations, like individuals, always need attentive stewardship; to sustain them we must recognize that they are fragile. Fail to see this and you're like Alexander the Great or a hubristic CEO. You believe you're immortal and divine, refuse to choose a successor, and leave your empire to be torn apart by vulturing generals.

In *How the Irish Saved Civilization*, Thomas Cahill writes about how those who lived in the Roman Empire in the earliest centuries AD took Rome as a proxy for the whole world. When it fell, the world seemed to. At the same time, it was exactly *because* so many—especially in the empire's outer reaches—believed the world was ending that they worked mightily to preserve Rome's achievements, so it might live on after death. The Irish monks, Cahill says, saw the writing on the wall and tirelessly copied Greek, Latin, and Christian manuscripts, starting in the fifth century, while archives on the European continent were lost forever to Visigoths. (The primitive bells of the doomsday-cult monks were called *cluigs*; *cluig*, with various spellings, is one source of the modern word *clock*.)

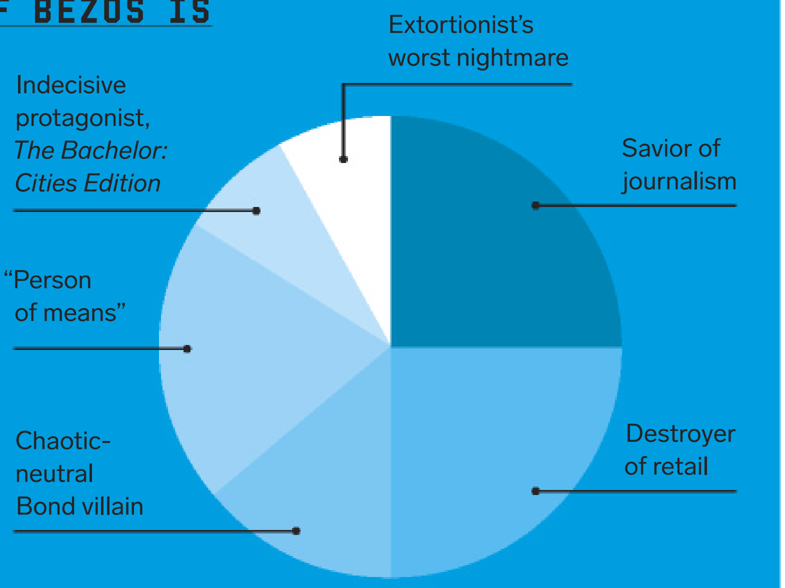
The crowd filed out of the Doomsday Clock's unveiling. I could have sworn they looked high. Thinking about death without, for the moment, actually dying is heady. Humans must surely be the only animals who contemplate doom, and as long as we do so, we are still human—and paradoxically not doomed.

VIRGINIA HEFFERNAN *(@page88) is a regular contributor to* WIRED.

CHARTGEIST

BY JON J. EILENBERG

WHAT JEFF BEZOS IS



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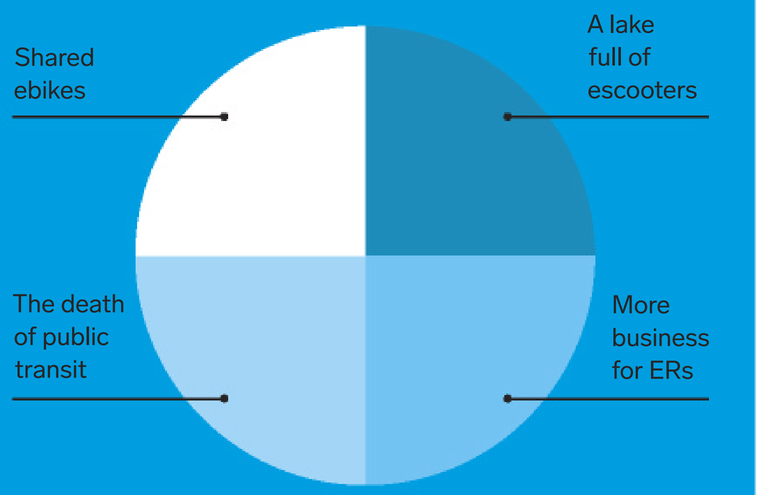

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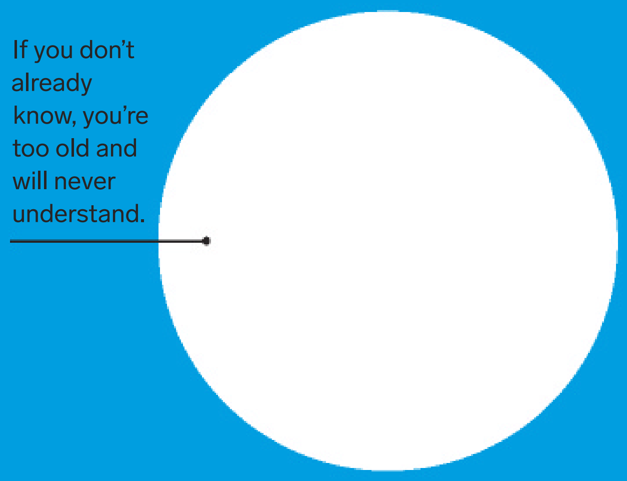

PRIVATE A.I.

Machines shouldn’t have to spy on us to get smarter.

BY ZEYNEP TUFEKCI

In old spy novels, when two secret agents need to communicate with each other out in the field, one of them often leaves a document in an assigned place—tucked in the hollow of a tree trunk or between the pages of a certain library book. Once the first agent has safely vacated the scene, the second one moves in to fetch it. ■ This maneuver—called a dead drop—may seem straightforward. But if you think about it, there’s a serious hitch: Somehow, the location of the dead drop has to be prearranged. ■ This isn’t just a problem with the genre conventions of spy thrillers. For thousands of years, this was, in fact, a fundamental flaw in human communication. Whether you were Caesar, Napoleon, or a spy using shortwave radio during the Cold War, if you wanted to communicate secretly in the future, you had to first manage to communicate secretly in the past. And arranging that moment of first contact ➜

ILLUSTRATION / STORYTK

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between two agents was always dangerous, difficult, and prone to interception.

Then in 1976, two privacy-oriented computer scientists, Whitfield Diffie and Martin Hellman, cracked this age-old problem with an idea called public key cryptography. They came up with an ingenious protocol that involved the use of one-way functions—mathematical calculations that are easy to solve in one direction but very, very difficult in the other. (It's easy to multiply two large prime numbers together to get a very large result, but it's super hard to work backward to find those original two numbers—unless you own billions of dollars worth of supercomputers. Hi, NSA!) Here's how it most often works in practice: One person, let's call her Alice, creates a *private* key, which gets fed through an algorithm using one-way math functions to create a *public* key. After that, anyone can send an encrypted message to Alice, and only she will be able to unlock it easily.

We need a new breakthrough in encryption, one that fundamentally changes the rotten trade-off we now make between privacy and AI.

The implications of this breakthrough have been vast. For most of human history, if anyone wanted to communicate secretly, they had to engage in a bunch of perilous, time-consuming, and expensive spycraft. That was the trade-off, the cost of doing business. Public key cryptography dramatically changed that. All of a sudden, in one swift revolutionary moment, people could communicate secretly *ab initio*—not only spies, but everybody. And it was fairly painless. Just think of all the confidential exchanges you conduct with strangers online: Every time you log in to a bank account or shopping site, browse an "https" web page, or send a digital signature, you're relying on a user-friendly version of private key cryptography. Diffie and Hellman didn't just render the dead drop obsolete; they made the internet as we know it possible.

Now consider another, more modern phenomenon that needs to be made obsolete—a data transaction that is very different from a dead drop but also terribly flawed.

Today, if you're a company that benefits from machine learning, chances are that, somewhere along the line, you've engaged in a bunch of nightmarish surveillance. Right now that's just the cost of doing business with this technology.

Machine learning, as you may have heard, is a computational method that involves training algorithms to recognize patterns in lots and lots of data until, eventually, they can answer questions, make predictions, and solve problems. For example, Google Translate works by chewing through billions of words of existing translated text—its "training corpus"—to generate the most probable correct translation. The results aren't perfect, but they can be uncannily effective.

They're effective enough, anyway, that the rush to capitalize on this form of AI has set off a feeding frenzy. Companies are collecting, scraping, mining, and buying every scintilla of data they can get their hands on. Unscrupulous third parties are doing even worse. Wherever lots of data is stored, there's a good chance it will be breached, pilfered, sold, hacked, and eventually fed into machine-learning protocols, sometimes for malevolent purposes. The technology's success is simultaneously a privacy-violating disaster for society.

At the same time, other pitfalls with today's machine learning hold it back from being useful where it might really help. For instance, it's a challenge right now for responsible actors to use machine learning in scenarios where it's not legally possible or ethically desirable to share underlying data. Say two hospitals each have a corpus of data about patient outcomes after initial Pap smears—a notoriously difficult diagnostic test for cervical cancer. Machine learning has shown some real promise at being able to read these tests. It might be highly beneficial to train an algorithm on the whole data set, but that would require bringing it all together somehow. Hospitals may not be legally allowed to share patient information. Their hands are tied.

So how do we preserve—and even expand—the benefits of machine learning while also reconciling it with basic standards of confidentiality? We need some new breakthroughs that fundamentally change the rotten trade-off we now make between privacy and AI. The good news is that there's a growing research effort in what's called "privacy-preserving" machine learning. Academics are trying to develop algorithms that can operate on encrypted data, which means they wouldn't need to access anyone's data directly. Other researchers are figuring out ways to combine insights from different machine-learning models without needing to merge all their underlying data. Companies like Apple, Google, and Microsoft already have teams working on such projects.

With effective regulation, those teams would grow faster. We should ban the spurious and excessive data collection that is currently the norm—not only to put a stop to obviously abusive practices, but also to speed innovation. When faced with new regulatory barriers, companies and researchers will pour effort into developing new compliant ways to have their cake.

With any luck, their breakthroughs will make it newly possible for, say, medical researchers to use machine learning on sensitive, private data sets—and for the rest of us to enjoy the perks of ubiquitous AI without having our privacy savaged. Those researchers' challenge, and ours, should be to render the headlines of the early 21st century (*Equifax hacked! Facebook data pilfered!*) obsolete. Heck, one day they may even seem quaint—like the bizarre practices of spies in old paperback novels.

ZEYNEP TUFEKCI *(@zeynep) is a* WIRED *contributor and a professor at the University of North Carolina at Chapel Hill.*

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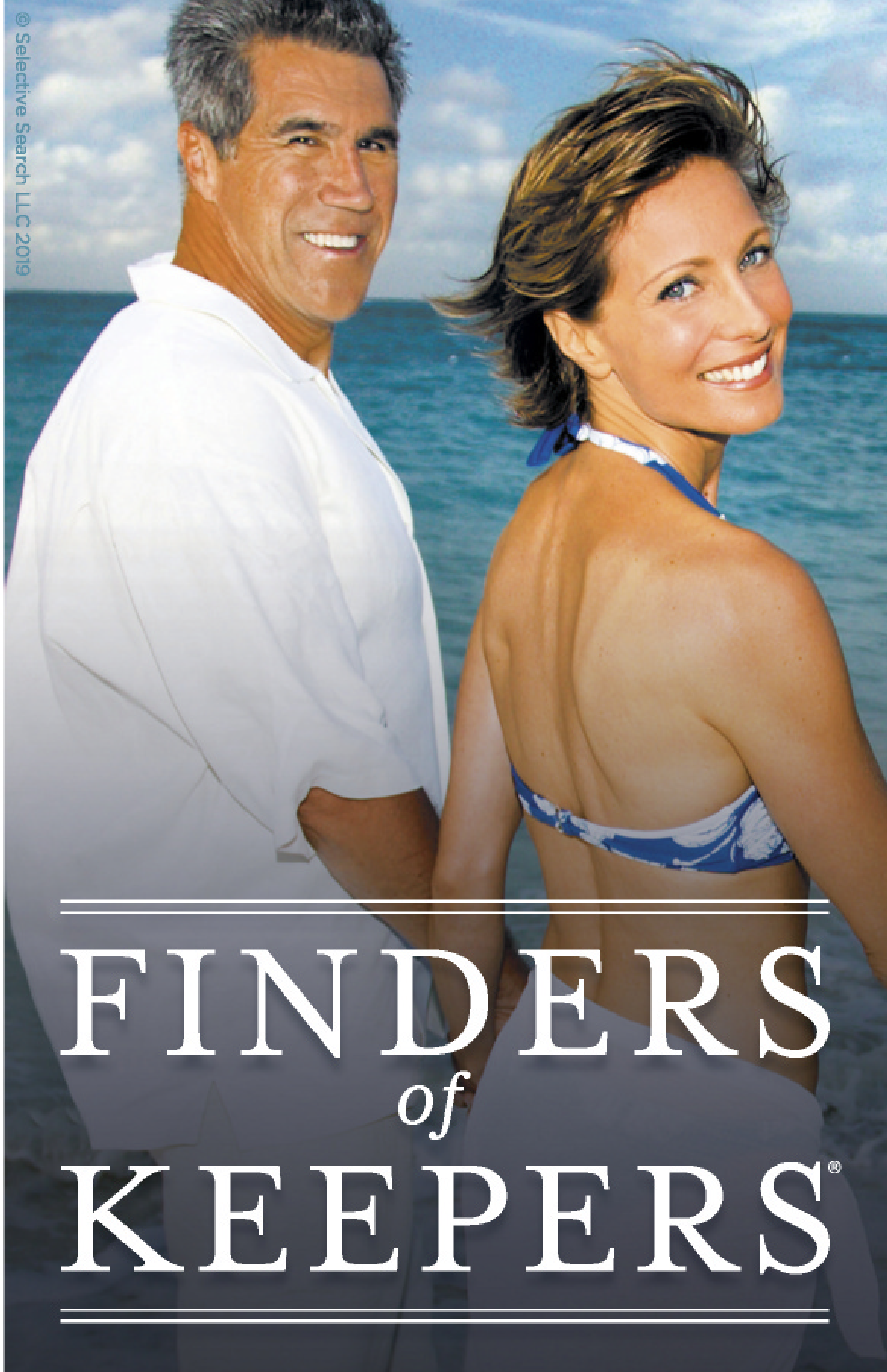

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SEIZE THE MOMENT

Americans have reached peak indifference on climate change. Time to do something about it.

BY CLIVE THOMPSON

Something weird is happening around climate change. Republicans are deciding it's real. Three years ago, only 49 percent of Republicans thought so, but by last December it was 64 percent, as a Monmouth University poll found. That's a huge jump in a short time and is all the more astonishing given that the Republican president and many of his party's politicians pooh-pooh the global emergency. Meanwhile, other parts of the electorate are really freaking out. Last year, the percentage of those who say they're "very worried" about global warming shot up from 21 percent to 29 percent, according to a poll by Yale's and George Mason University's programs on climate change communication.

Those who've studied this shift say it's because of the recent waves of unsettling, climate-related news. The problem is now knocking on everyone's front door: record-breaking heat and cold, ravaging hurricanes, rampaging wildfires in overdry forests. "It's not distant," says Anthony Leiserowitz, head of the Yale program.

There's a phrase I like that describes what's happening, and it helps us grasp what might be next: "peak indifference." It refers to the psychology of problems that become too big to ignore.

Peak indifference is a coinage of the sci-fi writer, blogger, and activist Cory Doctorow (who is, full disclosure, a friend). You can think of it this way: Often, when society is facing a problem that's terrible but slow-growing, we ignore it. We're *indifferent* to the problem. Climate change isn't the only example (think of digital privacy or income inequality), but it's perhaps the toughest to crack.

The psychologist Robert Gifford once enumerated the "seven dragons of inaction" on climate, from ingrained habits (car culture) to lack of trust (in, say, scientists) to numbness (statistics overload). As the crisis grows, our indifference grows too.

"You divert your energy from convincing people there's a problem to convincing them there's a solution."

But at some point, a crisis gets so bad that it becomes unignorable. Our indifference reaches a peak, begins to decline—and panic emerges. This could describe what we're now seeing in the climate polling. Media coverage and real-life events have finally broken through to folks: "Increasingly they're saying 'Wait a minute, this is happening right here, right now,'" Leiserowitz says.

This is great for anyone who wants to fix the problem, yes? Society is finally ready!

But Doctorow's theory also predicts another psychological hazard: When we ignore trouble for so long, we can slip quickly into nihilism. *It's too late. We missed our chance to take action.*

That means the current political moment is incredibly interesting. Anyone who wants to deal with climate change may have only a brief window to sell the public on a plan. In his new book *The Uninhabitable Earth: Life After Warming*, the writer David Wallace-Wells talks about the value of panic to pushing collective action; Doctorow says it's the point "where you divert your energy from convincing people there's a problem to convincing them there's a solution."

This is why the stakes are so high in the debate over the Green New Deal that Democrats recently introduced in Congress. The young environmental activists of the Sunrise Movement flooded DC this winter to push for a resolution. Six Democratic presidential candidates now support it in principle. And the Yale–George Mason survey found 81 percent of all Americans support the general concept, including—remarkably—57 percent of conservative Republicans. Clean energy policy "has a huge social consensus," Leiserowitz notes.

Still, barriers to action loom. More Republicans may believe in climate change, but they don't think it's caused by humans. And the Yale survey question about the Green New Deal was vague and upbeat, and didn't pose the tough-to-sell policy specifics (zero-emission transportation, job guarantees) or financial costs that the public might dislike. And even people terrified about climate change don't always agree on what policies to pursue. But the Sunrise activists, and all of us who want action on this, have to push hard *now*. It's only when you reach the peak that you can see where you need to go. ▣

CLIVE THOMPSON *(@pomeranian99) is a* WIRED *contributing editor. Write to him at clive@clivethompson.net.*

ANGRY NERD

BY JASON KEHE

THE NEXT BIG ONE

I have superpowers, OK? One of them is predicting earthquakes. Don't go showing me "government" "reports" disproving my awesome abilities. Twice already this year, I have shaken awake before my house has. So you will believe me when I tell you, unblessed mortals, that my seismological Spidey sense discerns a Third Event. This catastrophe won't involve literal tectonics. What I'm detecting is the quivering instability of the metaphorical. You know, the *platforms,* the slabs of virtual bedrock underlying my life. Entertainment platforms. Social media platforms. Delivery platforms. Dating platforms. Security platforms. Platforms—here's where meaning truly crumbles—*as a goddamn service.* Every day they shift beneath my feet. I wobble and sideways-leap, a manic hopscotcher, from one digi-plane to the next, deplatforming and replatforming, slacking to Zoom (cross-platform functionality!) with a stop for analytics and a detour through Twitch. One misstep and I'd slam into the cyberpavement. *Youch!* As if the landscape weren't treacherous enough, the coder-architects insist on layering on the AI, further unanchoring the ensmartened platforms from my control. Now Instagram must scroll through me. Picture the digital strata, if you can: AI platforms on top of software ecosystems built on hardware platforms resting on dead-tree-desk platforms. The metaphor can't survive the intercalations. The French *plateforme* literally *means* flat shape, but tech has no use for simple geometries. It must complexify and extra-dimensionalize, obscuring the dangers in steadying figurations. The AI-enabled, cloud-integrated, solutions-oriented platform of the future? Cute! Nonthreatening! Well, just you wait. It gathers mass. It's deeply unstable. The Big One won't crack open the earth. Look up, and out, for the dataquake.

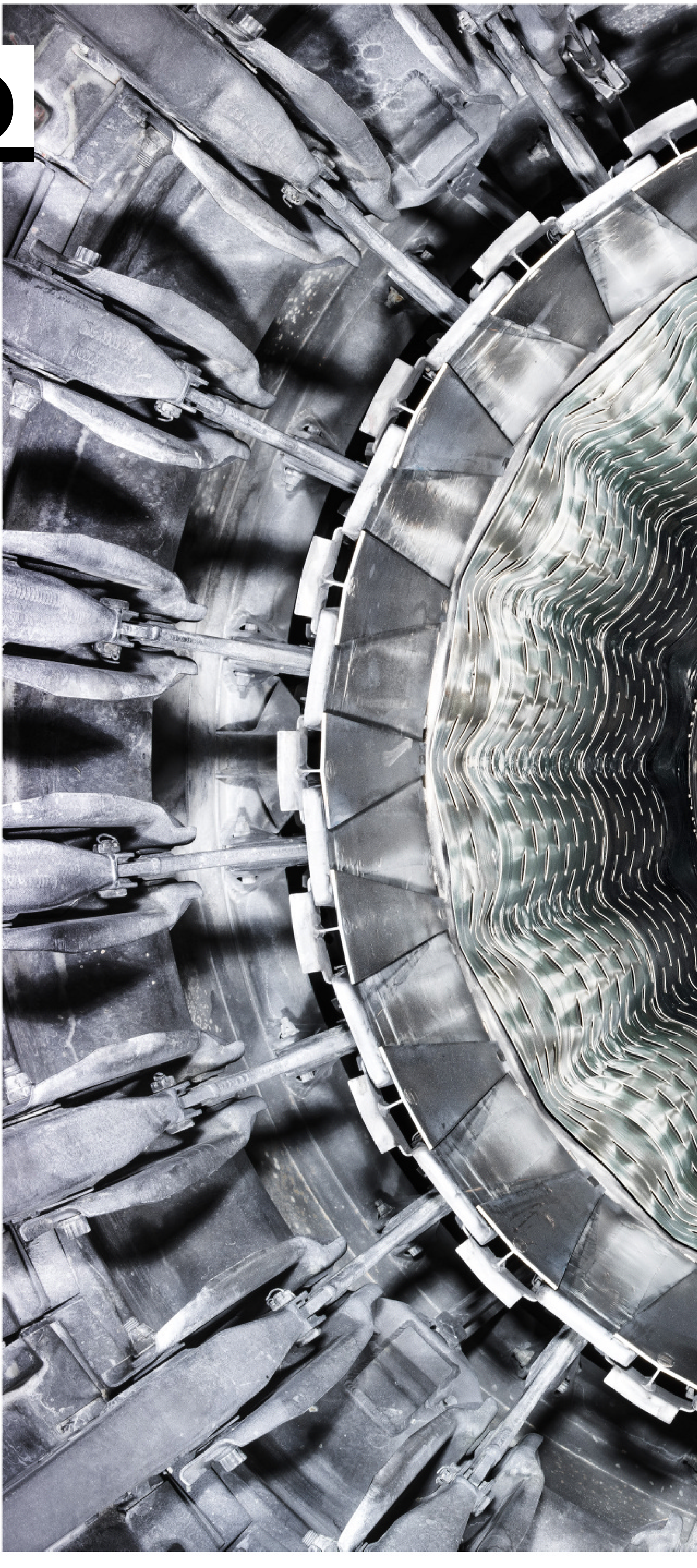
Getty Images (Fire and Lawn), Angry Nerd illustration by StoryTK

ILLUSTRATION / ALVARO DOMINGUEZ

VROOM TO SPARE

Propelling the fastest woman on four wheels.

BY LAURA MALLONEE

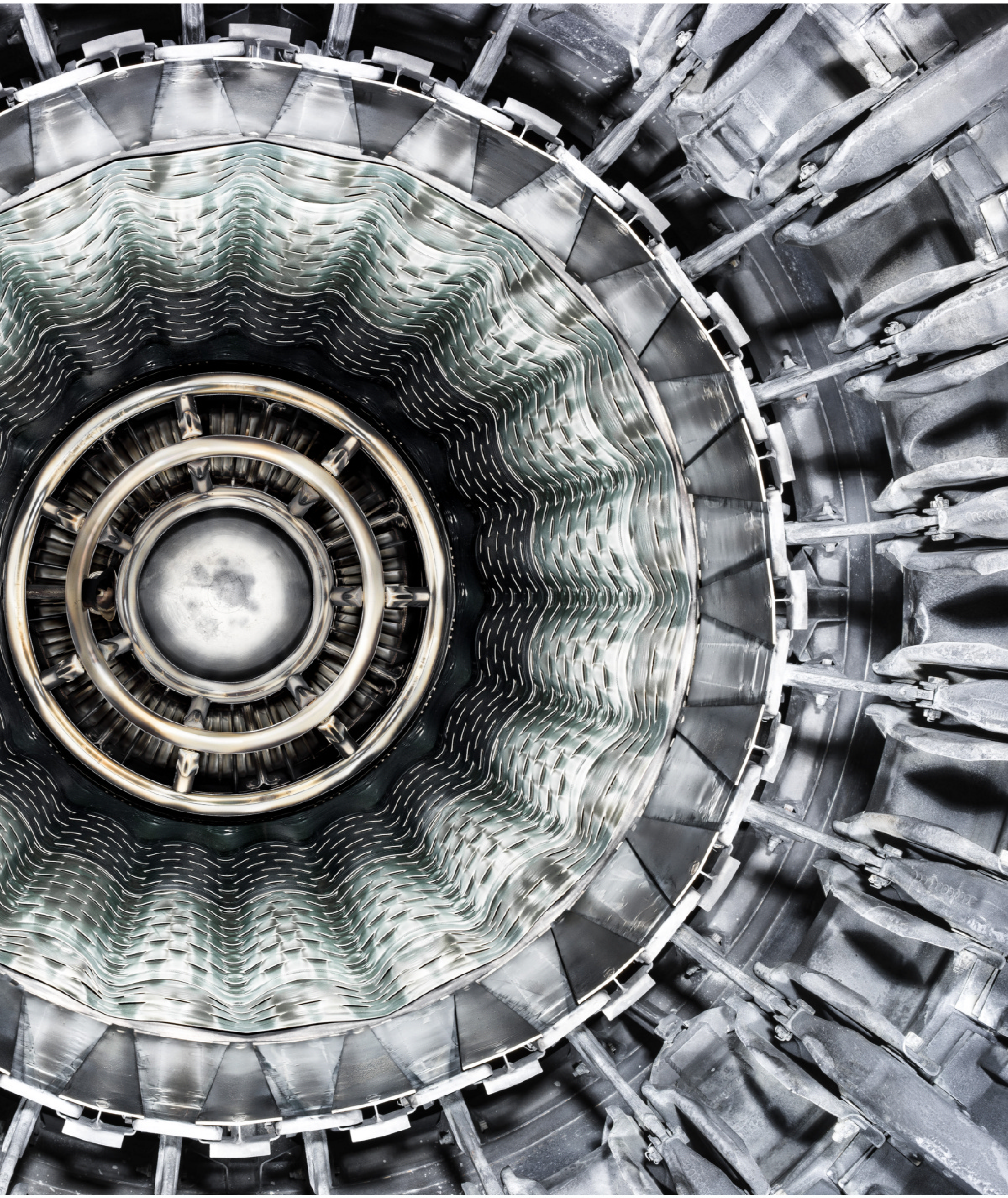


This hypnotic whirl of metal is the afterburner of a General Electric J79 axial-flow turbojet engine—the same engine used on F-4 Phantom jets, made by McDonnell Aircraft during the Vietnam War. But this one is mounted in the North American Eagle, a 56-foot-long supersonic aircraft turned racing car.

Six years ago, the engine got a new four-line afterburner that increased its muscle, giving it 19,000 pounds of thrust and 45,500 horsepower—enough to go 835 mph. In the past two months, it's been upgraded again to help race-car driver Jessi Combs take a shot at the womens' land-speed record. Stuntwoman Kitty O'Neil set the current record—512 mph—for a female driver way back in 1976. (British racer Andy Green has held the overall land speed record of 763 mph since 1997.) Tweaks include a vastly improved fire suppression system and a fuel filter off a Lockheed F-104 Starfighter to replace a DIYed one. The vehicle, like a jet, uses kerosene and drains 160 gallons of it every minute; the filter removes contaminants and improves flow to the engine so Combs can go as fast as she wants.

According to Keith Zanghi, CEO of the North American Eagle project, the only thing standing in the way of Combs' run is having a stable-enough strip of land. Last year, they got permission to use Diamond Valley's lake bed in Nevada, but the playa was too soft from winter snow to support the car's 14,500 pounds. This year, if it hardens up, Combs will take her shot between July and September.

Combs, 35, grew up in the Black Hills of South Dakota and has been racing cars since before she could legally drive. "I was born with a lead foot," she says. She rose to fame building off-road vehicles on Spike TV's *Xtreme 4x4* but left the show after a 550-pound band saw fell on her, fracturing her spine. After her recovery, she joined the North American Eagle team in 2013 and became its primary driver last September. Zanghi says she's simply "the most qualified person in the world" to helm the vehicle, having made more than a half-dozen test runs over 400 mph—a speed that Combs describes as "so fast it's slow, so loud it's quiet, so bumpy it's smooth."



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Ace of Hearts

The next step in wearables: sensors that watch for ticker troubles. —Lauren Goode

$130

WITHINGS MOVE ECG

I've long thought Withings wearables are the kind of smartwatches that most people actually want to wear. The French company eschews "wrist-computer" designs, opting instead for devices that look and feel like analog watches and—hallelujah!—don't need to be recharged every night. Withings' first smartwatch that tracked your activity, the Activité from 2014, even had "SWISS-MADE" emblazoned on it. Smartwatches have grown more sophisticated since then, thanks to an explosion in health-tracking apps and the proliferation of sensors to feed them. So even if you hate the battery-draining displays and toylike straps of nerdwatches, it's hard to beat their health-measuring features. Which is why Withings' Move ECG smartwatch caught my eye. Like its forebears, the new model appears to be simply a stylish watch, but it can record my walks, runs, swims, and snoozes. Daily steps are displayed on a small, secondary dial nestled into the watch face; everything else shows up in Withings' mobile app. Most notably, as the name suggests, the watch takes electrocardiogram readings from the wrist and can sense possible irregular heartbeats. And unlike the ECG-capable Apple Watch Series 4, which needs a daily recharge, the Withings uses a coin cell battery that lasts up to an entire year. But possibly the best thing about the Move is that it isn't yet another notification-blasting, attention-sucking screen to stare at. Be still, my heart.

PHOTOGRAPHS / DWIGHT ESCHLIMAN

TOP 3

Who's There

The latest video doorbells don't just connect your door to your phone. Control these with your voice, and let them govern the gadgets in your smart home. —Adrienne So

$199

RING DOOR VIEW CAM

If you live in an apartment building or a condo, you probably don't have a hardwired doorbell you can rip out and replace with a smart option. Good news then: Ring's new battery-powered Door View Cam slots into any existing peephole for an easy fix to that dilemma. Call up the feed from the motion-detecting camera through your phone or any Alexa-enabled device with a screen, and use the two-way talk feature to tell strangers to buzz off. If you pay for a $30 yearly cloud-storage subscription, you can check out videoclips from the last 60 days—helpful if you want to sneak a peek at your teen's comings and goings while you're out of town or take a gander at who has been sniffing around your bike shed.

$279

NEST HELLO

Nest's hardwired unit can use its computer vision technology to recognize faces. Train it by tagging friends and relatives in your videofeed, and the system will issue alerts when they arrive. It can announce them by name on your phone's screen or through any Google Home speaker. If a stranger shows up, you can keep things transactional with a quick, prerecorded greeting. Video from the Hello is clear, even with tricky shadows or at night, and the doorbell can stream continuous footage if you want to survey your stoop from afar. Just know that some of the advanced features require a Nest Aware subscription ($50 a year).

$299

NETATMO SMART VIDEO DOORBELL

Most door cams store footage in the cloud and require a subscription to access the captured clips. Instead, Netatmo's hardwired device records your footage onto a microSD card—no monthly fees required. It's compatible with Apple HomeKit, so you can set up a Siri Shortcut that turns on the smart light bulbs on the porch to illuminate both friends and foes. Of course, you can also ask your iPhone to show you who's outside. If they're holding a package, you can talk to them remotely through the built-in speaker: "Put the box down and back away slowly."

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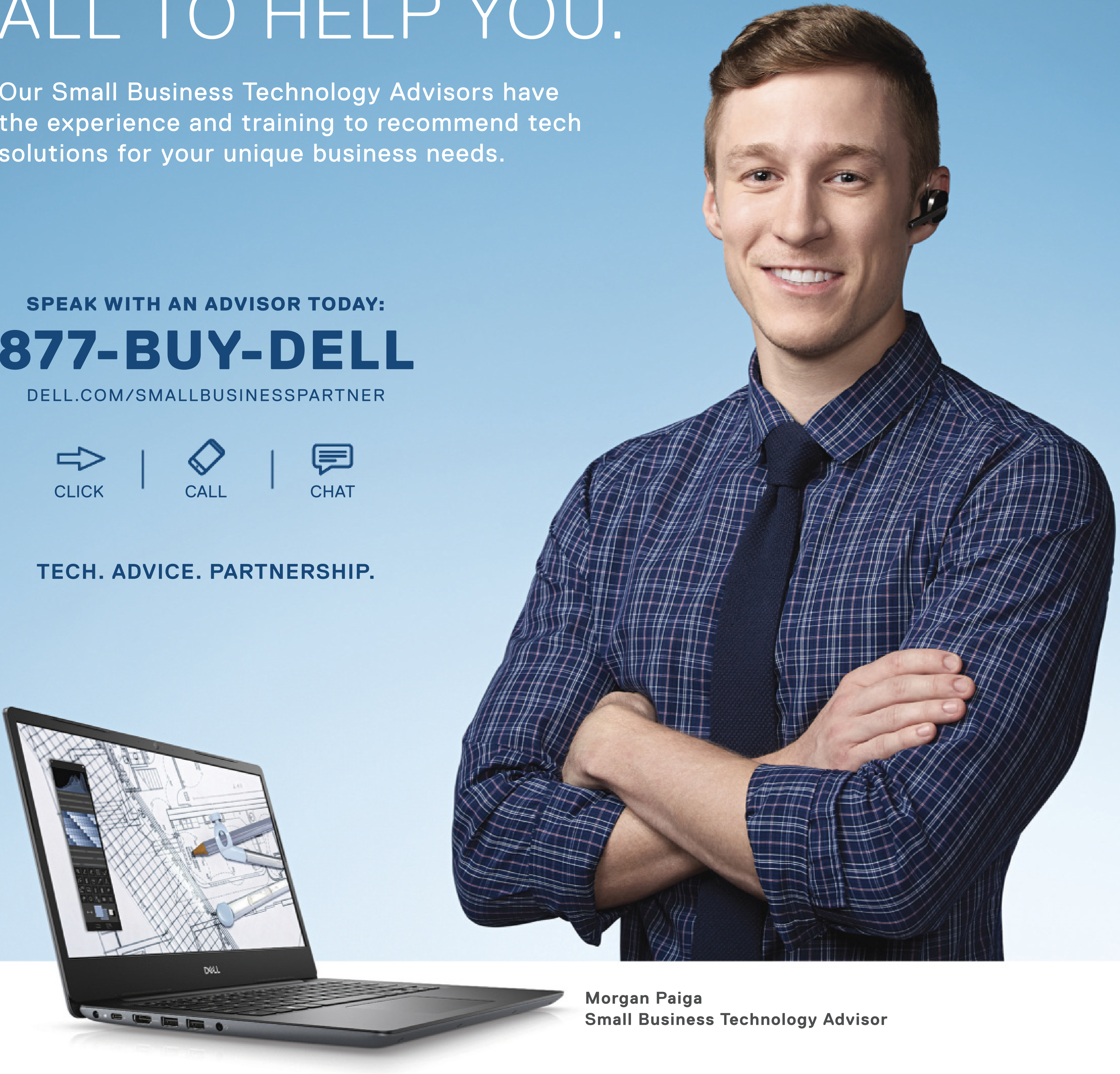

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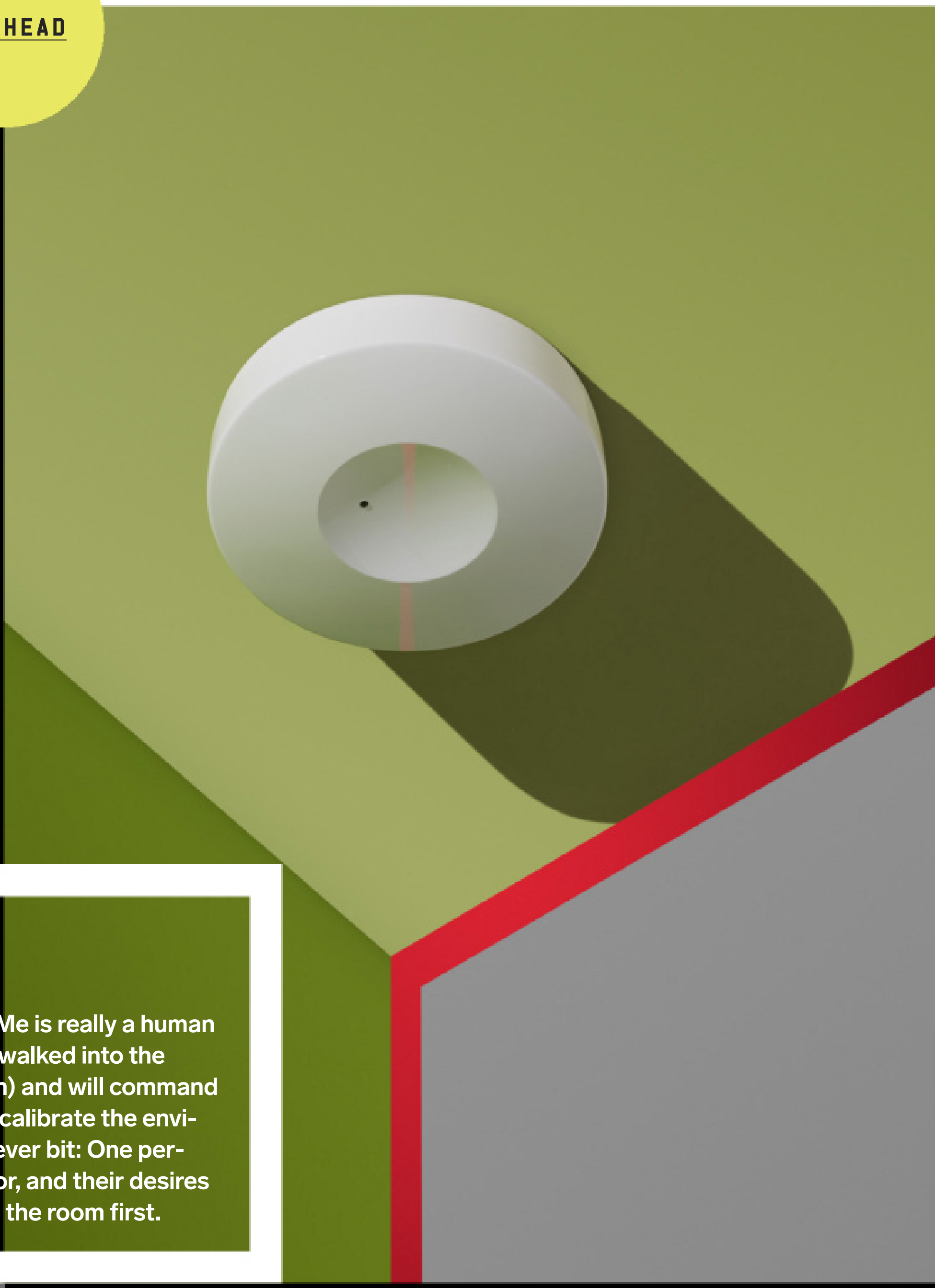
GEARHEAD

Residence Genius

You *can* teach an old house new tricks. Add convenience and energy-saving perspective to your home with these intelligent gadgets. —Michael Calore



INTELLITHINGS ROOMME

It may look like a smoke detector, but the RoomMe is really a human detector. The sensor-laden fixture can tell I just walked into the room (by sniffing my smartphone over Bluetooth) and will command connected thermostats, lights, and speakers to calibrate the environment to match my preferences. Here's the clever bit: One person gets to be the "Room Master" of each sensor, and their desires override everyone else's—no matter who was in the room first.

$70

EVE ENERGY STRIP

With this three-outlet, Wi-Fi-connected surge protector, you can introduce any lamp, fan, or appliance to the internet by simply plugging it in. In the accompanying app, users can program devices to go on or off by time of day or when Siri or some other smart device in the home pings them. Don't worry, such traffic is all end-to-end encrypted. The strip also collects power consumption data and plots it in easy-to-grok graphs.

$100

$1,100

IROBOT ROOMBA I7+

Onboard sensors help this robovac learn the layout of one's home. We can then look at the resulting floor plan in the app and create automated cleaning schedules—like, say, the kitchen every day and the hallway every other day. Our favorite new thing? Between sweep sessions, the Roomba empties its own dustbin into a bag in the charging station. The only thing we have to do is replace the bag after 30 cleanings.

$249

ECOBEE4

Any smart thermostat lets us set the temperature with an app, but this one has voice control: Ask its built-in Alexa to make it warmer or cooler, or to broadcast the latest news on your smart speaker. The wall-mounted unit comes bundled with a Zippo-sized Room Sensor; what's great about this is you can place it near where you hang out the most, like the sofa, so the thermostat can take accurate readings from that microclimate and not the one over by the wall.

$60

C BY GE C-START SMART SWITCH

This dimmer switch lets you control any light bulb, smart or not, with a touch, a tap in its app, or a voice command through Alexa or Google Assistant. Install multiple switches and control the lights in every room from any single switch. It's motion-sensitive too, but a Do Not Disturb mode will keep Poppy—my 10-year-old tortie—from running up my electric bill at night.

Night Moves

Devices claiming to deliver a more satisfying night's sleep keep materializing. Do we really need the help? —Arielle Pardes

Matteo Franceschetti began optimizing his life long before he started a tech company dedicated to sleep: heart rate monitored on an Apple Watch, a ketogenic diet, Peloton exercise bikes—one at home, one in the office. But sleep? The time he spent between the sheets felt, to him, unquantified and underutilized. Looking to squeeze more out of his unconscious hours, Franceschetti created Eight Sleep, to "unlock the full potential" of slumberland. The company's latest invention is a "smart mattress" that tracks every toss and turn, manipulates each sleep cycle, scores each night's rest, and then uses machine learning to "tune" the bed to your preferences.

Franceschetti's mattress ($2,295 for a queen size) hacks the whole sleep experience, starting with thermoregulation—warming as you drift off, then dropping a few degrees, he says, to extend the period of deep sleep. In the morning, the bed's "thermo alarm" cools you down just enough to speed up your heart rate and make you feel awake. Franceschetti believes these adjustments can help people get the amount of restorative sleep in six hours that would normally take eight: "That will account for six years of waking hours in your life."

Doctors have studied sleep for 50-odd years. They've learned, for instance, that we nod off better when warm but our bodies cool down during the dream state; that melatonin production is suppressed in blue light; and that sound stimulation called "pink noise" can deepen brain waves during deep sleep. Now their discoveries are trumpeted in an array of dreamy products. The Cambrian explosion of bedroom gadgets that began with wearables on the wrist and sensors under the sheets have become full-blown interventions.

Like the Eight mattress, a "self-learning superbed" called Bryte (starting at $5,950 for a queen) uses machine learning to adjust mattress temperature and firmness through the night. A "cuddlebot" called Somnox simulates calm breathing to lull you to sleep. Dreem Band and the Philips SmartSleep, both Jane Fonda-esque headbands, supposedly monitor your brain waves and pipe in dream music via bone conduction as you slumber. Even Casper, the mattress-in-a-box company, now traffics in hardware like Glow, a device that reimagines the bedside lamp as sleep tech. The wireless podlike light (pictured here—$89 for one, a pair for $169) gently dims at bedtime, then brightens in the morning to wake you up.

OK, wait. AI in our mattresses, pink noise mainlined into our skulls? Sleep used to feel as simple as closing my eyes; now I'm worried about all the ways I'm doing it wrong.

So I reached out to Christopher Winters, a neurologist and sleep specialist. The excitable and energetic Winters quickly calmed me: These gadgets are evidence of sleep medicine's "Gatorade moment," he says. When sports doctors discovered the benefits of electrolyte replenishment during workouts, Gatorade rapidly became something we could drink for a more vigorous life—never mind that most of us get on fine with water alone. Sleep research, Winter adds, is being "bottled, packaged, and put out to the masses." He also reminds me that many of us sleep fine without it all.

Yet by some estimates, sleep tech has grown into a $76 billion industry. Why are we drinking the sleep-tech Gatorade? Well, the promise of spending less time asleep and waking up with more energy is tantalizing. (I'd learn Japanese, write a book, bone up on every candidate running in 2020.) More important: For those who do suffer restless nights, such devices might provide some relief and even prevent real disorders. But for the rest of us, these gadgets are an expensive solution to a nonexistent problem. Sometimes, just counting sheep is enough.

ARIELLE PARDES *(@pardesoteric) wrote about demetrication in issue 27.03.*

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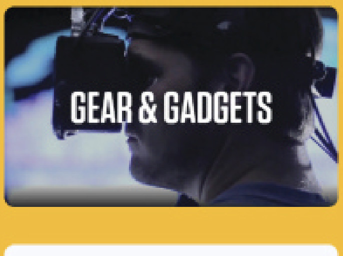

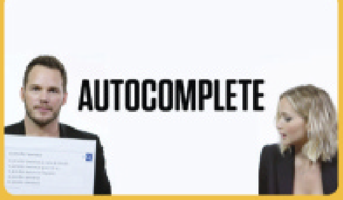

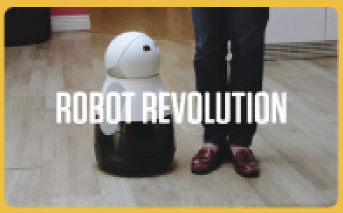

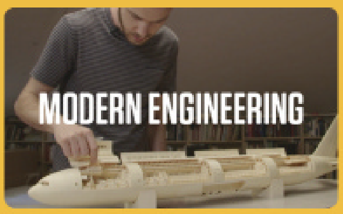

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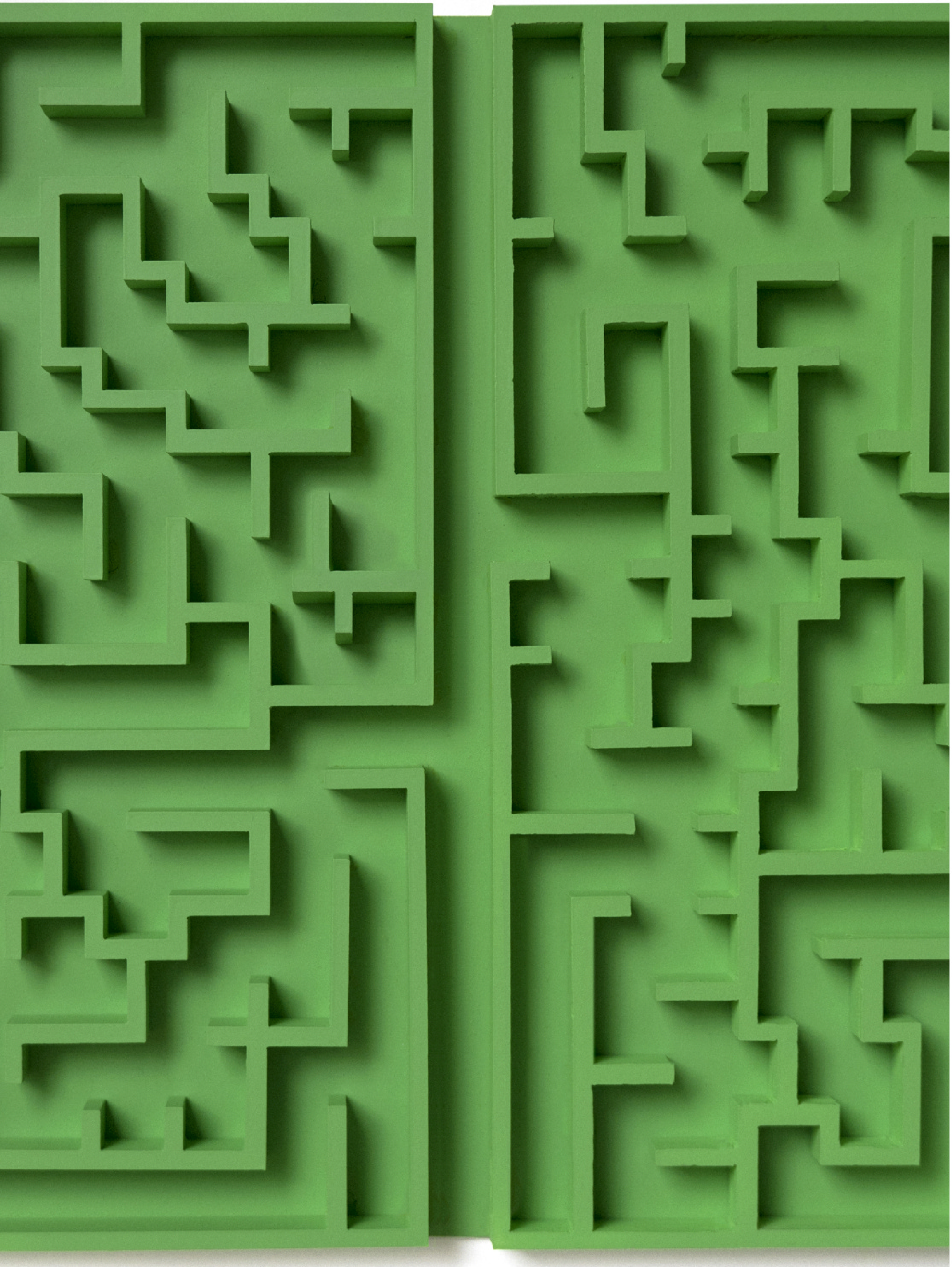


PHOTOGRAPH / DELCAN & CO

EFFICIENCY IS BEAUTIFUL

For coders, lack of friction is an aesthetic joy, an emotional high, the ideal existential state. It's what drives them—and what shapes our world.

BY CLIVE THOMPSON

Shelley Chang was working as a business analyst for a computer company in 2010 when she met Jason Ho through some mutual friends. Ho was tall and slender with a sly smile, and they hit it off right away. A computer programmer, Ho ran his own company from San Francisco. He also loved to travel. Less than a month after they met, Ho surprised Chang by buying a plane ticket to meet her in Taiwan, where she'd temporarily relocated. Soon they were talking about visiting Japan together for four weeks. Chang was a bit apprehensive; they didn't know each other well. But she decided to take the gamble.

Ho, as it turned out, had a very strict and peculiar itinerary planned. He's fond of ramen dishes, and to fit as many as possible into their visit to Tokyo, he'd assembled a list of noodle places and plotted them on Google Maps. Then he'd written some custom code to rank the restaurants so they could be sure to visit the best ones as they went sightseeing. It was, he said, a "pretty traditional" algorithmic challenge, of the sort you learn in college. Ho showed Chang the map on his phone. He told her he was planning to keep careful notes about the quality of each meal too. "Oh wow," she thought, impressed, if a bit wary. "This guy is kind of nuts."

Ho was also witty, well read, and funny, and the trip was a success. They ate a lot of ramen but also drank beer ringside at a sumo wrestling match, visited the Imperial Palace, and stopped by the hotel where *Lost in Translation* was filmed. It was the beginning of a seven-year relationship.

Oddities like the ramen optimizer have been part of Ho's daily routines for years. As a kid growing up in Macon, Georgia, Ho owned a Texas Instruments TI-89 calculator, he told me. One day while leafing through the instruction manual, he discovered that the calculator contained a form of the Basic programming language and taught himself enough to painstakingly re-create Nintendo's *The Legend of Zelda* game on the calculator. He learned Java on the computer and, after high school, went to Georgia Tech in Atlanta to study computer science. Abstract algorithmic concepts were interesting enough, but what really got him going was using computers to avoid repetitive labor. "Anytime I have to repeat something over and over," he told me, "I get bored."

In his final year of college, Ho started a company that created forums where students studying the same courses at different colleges could answer one another's questions. But it didn't amass nearly enough users, so he shut it down. He interviewed at a few companies like Google and Microsoft but sank into a funk. He didn't want to work for someone else. As a question of value creation, being an employee was a terrible proposition, he felt. Sure, you earned a check. But most of the value of your labor was captured by the founders, the ones who owned equity. He had the skills to build something, soup to nuts. He just didn't know what.

A few months later, he stumbled into an idea on a visit home to Macon. He went to Staples on an errand with his dad, a pediatrician who ran his own office. Ho's father needed to buy two time clocks, those old-school machines where employees insert cards to be stamped with the time they start—and stop—work for the day. Each clock cost around $300.

Ho was astounded: Had time-clock technology not changed since *The Flintstones*? "I can't believe this is still a thing," he thought. He realized he could quickly cobble together a website that performed the same task, but better: Employees could check in with their phones, and the site would total up the hours automatically. "Don't buy this time clock," he told his father. "I'm going to code you one." Three days later, he had a prototype. His father's office began using the service and, to Ho's delight, they loved it. The system was remarkably more efficient than a paper-based time clock.

He spiffed up the website, gave it a name—Clockspot—and, four months later, a law firm signed on as a client. When its first payment came through, Ho nearly jumped out of a chair at the Georgia Tech library where he was working. He was getting money for his software! Nine months later, Ho's company was earning around $10,000 a month from cleaning companies, home-health-care-aide firms, the city of Birmingham, Alabama. He worked nonstop for two years improving and debugging the code. Eventually he got it working so well that Clockspot was running mostly on autopilot. Besides himself, the only employee Ho needed was a part-time customer service agent. He was making a healthy income and had plenty of time for his travels and other interests. He'd optimized his life efficiency.

Like any sentient person, you've noticed that software is eating the world, to use venture capitalist Marc Andreessen's famous phrase. You've seen Facebook swallow the public sphere, Uber overhaul urban transportation, Instagram supercharge selfie culture, and Amazon drop off your shopping within 24 hours. Technological innovators generally boast that their services change the world or make life more convenient, but underpinning everything they do is speed. Whatever you were doing before—hailing a cab, gossiping with a friend, buying toothpaste—now happens faster. The thrust of Silicon Valley is always to take human activity and shift it into metabolic overdrive. And maybe you've wondered, why the heck is that? Why do techies insist that things should be sped up, torqued, optimized?

There's one obvious reason, of course: They do it because of the dictates of the market. Capitalism handsomely rewards anyone who can improve a process and squeeze some margin out. But with software, there's something else going on too. For coders, efficiency is more than just a tool for business. It's an existential state, an emotional driver.

Coders might have different backgrounds and political opinions, but nearly every one I've ever met found deep, almost soulful pleasure in taking something inefficient—even just a little bit slow—and tightening it up a notch. Removing the friction from a system is an aesthetic joy; coders' eyes blaze when they talk about making something run faster or how they eliminated some bothersome human effort from a process.

This passion for efficiency isn't unique to software developers. Engineers and inventors have long been motivated by it. During the early years of industrialization, engineers elevated the automation of everyday tasks to a moral good. The engineer was humanity's "redeemer from despairing drudgery and burdensome labor," as Charles Hermany, an engineer himself, wrote in 1904. Frederick Winslow Taylor—the inventor of Taylorism, which helped lay the groundwork for manufacturing assembly lines—inveighed against the "awkward, inefficient or ill-directed movements of men." Frank Gilbreth fretted over wasted movements in everything from bricklaying to vest buttoning, while his industrial-engineering partner and wife, Lillian Evelyn Gilbreth, designed kitchens such that the number of steps in making a strawberry shortcake was reduced "from 281 to 45," as *The Better Homes Manual* enthused in 1931.

Many of today's programmers have their efficiency aha moment in their teenage years, when they discover that life is full of blindingly dull repetitive tasks and that computers are really good at doing them. (Math homework, with its dull litany of exercises, was one thing that inspired a number of coders I've talked to.) Larry Wall, who created the Perl programming language, and several coauthors wrote that one of the key virtues of a programmer is "laziness"—of the variety where your unwillingness to perform rote actions inspires you to do the work to automate them.

Eventually that orientation toward efficiency becomes hard to turn off. "Most engineers I know go through life seeing inefficiencies everywhere," Christa Mabee, a coder in San Francisco, once told me. "Inefficiencies boarding your planes, whatever. You just get sick of shit being broken." She'll find herself walking down the street wishing people navigated the sidewalks and street crossings in a more optimal fashion. Jeannette Wing, a professor of computer science who runs the Data Science Institute at Columbia University, popularized the phrase *computational thinking* to describe what Mabee was talking about. It involves the art of seeing the invisible systems in the world around you, the rule sets and design decisions that govern how we live.

Jason Ho had a knack for seeing and trying to perfect those invisible systems. I met Ho and Chang in—of course—a ramen restaurant in San Francisco a few years ago. Ho was managing Clockspot, though it was ticking along so nicely by that point that he was working only a few hours a week. "He says he works 20 hours a month, but I don't think I've seen him work that much," Chang said. (The couple has since broken up, but the two remain on good terms.) Ho spent quite a bit of time traveling; once he'd even handled a Clockspot outage while at base camp on Mount Everest.

His optimizing and coding work, however, never stops. When he decided to buy a house, he wrote a piece of software into which he could dump the information for scores of homes on the market—their locations, prices, and neighborhood statistics—and the program would calculate the properties' probable long-term value. The program's top pick was a modern condo in Nob Hill. He duly bought it. Because he hates shopping, he bought dozens of pairs of the same T-shirt and khakis, a classic strategy for coders, since it removes the friction of decisionmaking when getting dressed.

A few years ago, Ho decided to take up bodybuilding, which presented a particularly demented optimization challenge: How ripped could he get? He carried a small scale to restaurants and weighed his food portions. "He tracked every single thing he ate in this massive spreadsheet," Chang said. Ho sheepishly showed me the spreadsheet on his phone; a sprawling beast that plotted every ingredient in his workout meals, for a total of 3,500 calories per day. He worked out in a gym but also devised ways to squeeze exercise into whatever he was doing. If he passed a thick metal railing, he'd use it to do pull-ups; if he passed a dumpster, he'd lift it up on one edge.

After two years of training, he placed second in an amateur bodybuilding competition. He flipped through his phone to find pictures of himself from the period. In one picture he's lightly oiled and posing in his underwear before a sunny window. He looks like a Greek statue. "I was down to about 7 percent body fat," he said. It felt good to look so ripped, he said, but mostly he'd just wanted to see whether it was possible.

Ho showed me another chart he'd constructed. This one was a life guide, of sorts, a way of optimizing not just his body but how he devoted every waking second. He decided he wanted to spend time doing only the things where every ounce of effort was most likely to produce maximum results. He'd made 16 rows labeled with life activities. Among them: entrepreneurship, programming, guitar, *StarCraft*, shopping, and "spending time with friends and family."

Then, in columns, he plotted various criteria—like whether the activity is inherently meaningful and not just a means to an end ("autotelic"), whether it "can be mastered," whether it "impacts multiple areas of life."

Jason Ho, founder of Clockspot, tries to make his life activities more efficient with code. "Anytime I have to repeat something over and over, I get bored."

> The orientation toward efficiency becomes hard to turn off. For some coders, people and their incessant demands can be a pain in the butt, and human relations another daily hassle to be optimized.

Adapted from Coders: The Making of a New Tribe and the Remaking of the World *by Clive Thompson, to be published March 26, 2019, by Penguin Press, an imprint of Penguin Publishing Group, a division of Penguin Random House LLC.* CLIVE THOMPSON *(@pomeranian99) is a* WIRED *contributing editor.*

PHOTOGRAPH / CAYCE CLIFFORD

For "programming" and "entrepreneurship," Ho ticked off *yes* for every quality. When he came to the social realm of "spending time with friends and family," he checked the box for "impacts multiple areas of life." For "can be mastered," he wrote *maybe*.

For a lot of people, this might seem nuts. The idea that you might want to systematize the emotional parts of life and regard social activity as a source of inefficiency is, to many people, discomfiting. Ho is gregarious and outgoing, but for some coders, people and their incessant demands can be a pain in the butt, and human relations another daily hassle to be fixed. It's a problem that technologists, back in the early days of computing, pondered with some unease. As Konrad Zuse, the German civil engineer who built the first programmable computer, was credited with saying: "The danger of computers becoming like humans is not as great as the danger of humans becoming like computers."

I thought of this one evening when I was engrossed in a Quora thread in which dozens of coders shared tales of how they'd automated the nuances of everyday life. There were some unsettling, if morbidly fascinating, ploys for turning social contact into a set-and-forget robotized task. "I got tired of hearing 'You never message me' from friends and family," one programmer wrote, so he created a script that would randomly send them texts, created using a Mad Libs–style mashup. A text would begin with this gambit—"Good morning/afternoon/evening, Hey {name}, I've been meaning to call you"—and then append one option from a list of endings: "I hope all has been well/I will be home later next month love you/let's talk sometime next week when are you free."

At a hackathon in San Francisco, a middle-aged coder excitedly showed me an app he'd created that would send automated romantic messages to a partner. "When you don't have enough time to think about her"—yep, he assumed the emotionally needy partner would be a her—"this can take care of it for you," he enthused. These sorts of attempts to make socializing efficient go all the way up the chain to the biggest high-tech firms: Think of Gmail's auto-complete feature, which encourages us to speed up email by having an algorithm compose our responses for us.

Linguists and psychologists have long documented the value of phatic communications—the various emotional devices humans use in everyday life to make others feel at ease or listened to: "How's it going?" "Crazy weather, eh?" "What are you up to tonight?" The more I talked to coders, the more stories I heard of people who found that stuff as irritating as grit in gears.

Christopher Thorpe, a veteran of more than a half-dozen tech firms, told me about "an incredibly talented engineer" he once worked with who fit that bill. "He was very upset with me that we told jokes in all our meetings, because we were wasting time. 'Why are we spending five minutes having fun with 20 people in the office? This is *work* time.' Everybody is laughing—but, you know, you're wasting all this valuable time." The joke had frittered the time of 20 people! This guy would begin rattling off the math: "Five minutes times 20, that's like, you know, *you've wasted an hour and a half of person-time on these jokes*."

Sometimes the most productive programmers are those who *reduce* code bases. Programming is reminiscent of poetry, where compression can confer power.

The truth is, I have some sympathy for coders' mania for optimizing daily life, because I've tasted those electric thrills myself. Three years ago I started working on a book about the psychology of programmers, so I decided to pick up the long-discarded coding I'd done on VIC-20s back in the '80s and dabble in some modern languages like Python and JavaScript. The more I played around writing little scripts, the more I began to notice, and be deeply annoyed by, moments of inefficiency in my daily affairs. While writing, for example, I'd find myself frequently consulting various online thesauri. (Feel free to judge me.) They were useful but so sludgy that each time I did a search it took maybe two seconds to load the results. So I decided to write my own command-line thesaurus, using a site that offered a thesaurus API. After a quick morning of tinkering with Python, I had a script. I'd type a word into the command line and get synonyms and antonyms back with lightning speed. It was green text on black, unadorned, and crude. But damn, it was fast: No more waiting around for the browser to load a slurry of tracking scripts while cookies clogged up my hard drive.

Granted, the amount of time this saved me was not terribly consequential. Assuming I search for synonyms twice an hour on average while I'm writing, and assuming (generously) that my creation saved me a rollicking two seconds per search, I spared myself, maybe, one hour a year of irked waiting. Hardly worth mentioning. Still, the burn of velocity warmed my soul. Each time I searched for a synonym, the zippy results produced a surge of pleasure. I was applying the drug of efficiency to my veins, and it felt good.

Before long I'd gotten addicted to writing code for little routines. I made one to clean up YouTube transcripts that I'd downloaded; another to crawl and archive links I posted to Twitter; one that continually checked the website of my son's elementary school and texted him when the teacher posted homework. (He was sick of hitting Refresh.)

A lot of my little programs were badly written, barely functioning hack jobs; I picked the most simple, brute-force way to get it done. When I looked at the code of really experienced programmers, I'd admire how much more elegantly they wrote. I'd come up with a sprawling, ugly function to sift through some data and then find that an experienced programmer could do it in a few crisp lines. (And their code ran a lot faster too.) Journalists sometimes marvel at the huge size of Google's code base—2 billion lines!—as an indication of its might. But coders aren't impressed by volume. Sometimes the most productive programmers are those who *reduce* code bases, make them shorter and denser. After three years at Facebook, an engineer named Jinghao Yan checked all of his contributions to the company's code base and found that the math was negative. "I've added 391,973 lines to and removed 509,793 lines from the main repository," he wrote on another Quora coder thread. (There are a *lot* of programmers on Quora, as it turns out.) "So if I coded 1,000 hours a year, that's about 39 net lines removed per hour!"

Programming is reminiscent of poetry, where compression can confer power. "In a well-crafted poem, every single word has meaning and purpose," as the coder and writer Matt Ward wrote in an essay for Smashing Magazine. "A poet can spend hours struggling for just the right word, or set aside a poem for days before coming back to it for a fresh perspective." Among the most famous modernist poems, inspired by the age-old concision of haiku, was Ezra Pound's "In a Station of the Metro":

The apparition of these faces in the crowd; Petals on a wet, black bough.

"In just two lines and fourteen simple words," Ward notes, "Pound paints a striking image, ripe with meaning and begging to be devoured by scholars and critics. Now, that's efficiency."

Back in 2016, I visited Ryan Olson, a lead engineer for Instagram. His team had just pushed out the platform's Stories function. It was a massive update. Olson told me about traveling around San Francisco in a blur of exhaustion mere hours after the update went live and seeing people already using Stories. "It's a pretty cool experience," he said. "Last night I was at the gym, and I looked over and someone is using the product. I don't know if there's ever been historically any other way where you could reach so many people" or where "so few people define the experience of so many."

It's one thing to optimize your personal life. But for many programmers, the true narcotic is transforming the world. Scale itself is a joy; it's mesmerizing to watch your new piece of code suddenly explode in popularity, going from two people to four to eight to the entire globe. You've accelerated some aspect of life—how we text or pay bills or share news—and you can see the ripples spread outward.

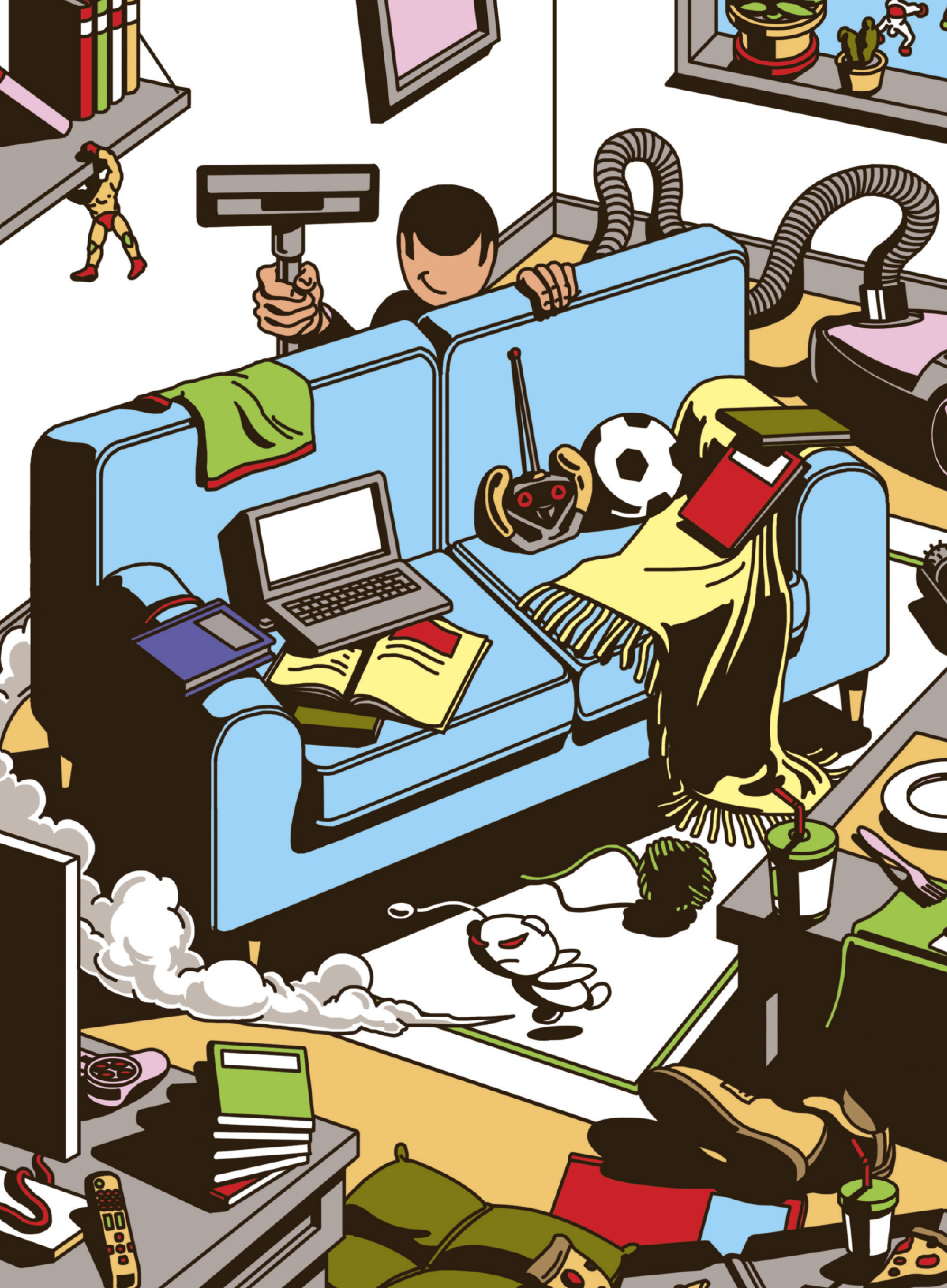
This is how the big riches in software are often made, too, so there's a concomitant frisson of power and wealth. Venture capitalists pour money into things they think will grow like kudzu, and the markets reward it. This nexus of motivations tends to produce, in efficiency-loving Silicon Valley engineers, not just a pleasure in scale but an absolute lust for it.

Indeed, among the royalty of Silicon Valley there's often a sort of contempt for things that don't scale. Smallness can seem like weakness. A few times while talking to tech bigwigs, I'd mentioned Jason Ho's company, explaining how I found it a smart and admirable business, a perfect example of an entrepreneur nailing an unmet need. But they scoffed. To them, Ho's Clockspot was a "lifestyle business"—Valley-speak for an idea that will never scale into the stratosphere. That sort of product is fine, sure, they say, but Google could copy it and put him out of business in a second.

Obviously we've benefited enormously from software engineers' twitchy, instinctive desire to speed things up, to create plenitude. But the simultaneous, relentless drive for efficiency at scale has troubling side effects. Facebook's News Feed speeds up how friends show us photos but also how malcontents spread disinformation. Uber optimizes car-hailing for riders but upends the economics of making a living as a driver. Amazon prepares drones for delivery of electronics over main streets denuded of stores.

Perhaps we—the folks whose lives are being so relentlessly optimized—are finally noticing these repercussions. We're certainly complaining more about Big Tech, noticing how it outgasses civic problems, how it enrages while it enchants. We don't quite know what to do about it; we still like the convenience, the way software constantly claims we can do more with less. But the doubts are prickling at our skin.

Maybe we're becoming uncomfortable with how we, too, in our daily habits, have embraced the romance of hyperoptimization. Look at the scene on any city street: Employees listening to podcasts at 1.5X speed while racing to work, wearing Apple Watches to ensure they're hitting 10,000 daily steps, peeking at work email under the dinner table. We've become like the coders themselves, torquing every gear in our lives to remove friction. Like any good engineer, we can make the machines of our lives run awfully fast, though it's not clear we're happy with where we're going.



"YOU COULDN'T PAY ME TO DO THAT."

The punishing ecstasy of being a Reddit moderator.

BY ROBERT PECK

These are the rules: Users of /r/aww aren't allowed to post about dogs that are dying, or sick, or just back from the vet. No posts about cats just adopted off the street; no bird-with-an-injured-beak stories. Cheerful descriptions of animals, however, are very much on point. Accompanying an image of a huge dog in a car's passenger seat: "This is Ben. He has a beard. And he is human sized. We get fun looks in traffic." Next to an image of a cat under elaborate blankets: "Our cat is obsessed with blanket forts, so we made him this."

These standards of adorable positivity are important to me, because I'm one of the moderators of /r/aww, the cute animal subreddit. In case that seems trivial, allow me to remind you of how powerful pet memes are online: As of this writing, the page has 19 million subscribers, and it's growing fast. Across the other subreddits that I moderate—/r/pokemon, home to a litany of imagined monsters; /r/PartyParrot, home to dancing birds—I oversee a couple million more subscribers. My job is to make and enforce rules for all of them.

Before these, I watched over other subreddits: /r/food, /r/Poetry, /r/LifeProTips, and dozens more. I got my first Reddit mod job, overseeing /r/pokemon, in 2014, when I was a senior in college. The volunteers put out a call for people to join their ranks, and I applied, writing that I wanted to bulk up on meaningful hobbies before I joined the world of full-time work. A week later, I was taken in.

There are less than 500 paid employees at Reddit, but tens of thousands of us volunteer moderators, for 14 billion pageviews a month. (Advance Publications, which owns WIRED's publisher, Condé Nast, is a Reddit shareholder.) My peers and I see every post and comment that comes in, one by one. We check every one against each subreddit's rules. Our rules.

ILLUSTRATION / MAXIME MOUYSSET

At /r/aww, people don't always submit pictures of kittens and puppies. Sometimes they post gore porn, or threats to find me and hurt me. My rules are both obvious (kittens are great; no gore porn, no threats) and designed to prevent misuse of the platform (no social media links or handles, and no spamming). At /r/pokemon, I block pictures of, say, caterpillars, because those aren't Pokémon, are they? No, no, they aren't.

/r/aww is the 10th largest subreddit. Every one of the 19 million people there is pseudonymous, and many abuse their relative anonymity. But there are also of course the good users, our singing birds. Like /u/Shitty_watercolour, a user who paints scenes that come up in the comments and then posts them. Or /u/Poem_for_your_sprog, the user who appears without warning and replies to posts exclusively in verse.

Once, on /r/AskReddit, someone invited health inspectors to describe the worst violations they'd ever seen. A user named /u/Chamale responded with a story. "My stepdad used to be a baker," Chamale began. The stepdad's bakery was an authentic re-creation of an 18th-century French fortress, and one day a health inspector came by; she was initially wary of the stonework walls and the doorless entryways, but the stepfather was able to convince her that these 18th-century touches took nothing away from his commitment to the highest health standards. Then, as the inspector was ending her visit, she walked into a doorless building attached to the bakery. There stood an escaped cow licking all of the bread loaves.

Soon, this reply came from /u/Poem_for_your_sprog:

my name is Cow,
and wen its nite,
or wen the moon
is shiyning brite,
and all the men
haf gon to bed –
i stay up late.
i lik the bred.

Reddit has been called a lot of things: a "vast underbelly," a "cesspool," "proudly untamed." And it is complicated. But it's the good parts that I'm here to protect.

By sharing popular photos of, say, dogs hugging over a fence, scammers hope that you will appreciate them, upvote them, and share them, and in so doing lend their zombie account further appearance of credibility.

It's not enough to take away a zombie's privileges, to warn it to play nice. It's a zombie. Kill it.

Courtesy of Oranit Kittragul

Sometimes that means fighting zombies. Across Reddit, unused accounts pile up, the ghostly remains of a million people who have just tried out the site for a day and then given it up. What you have to look out for is when these older accounts, long since dead and forgotten, suddenly come to life—because they can be dangerous.

One night I came across a post submitted by a user named /u/MagnoliaQuezada. The title of the post was “I miss you so much,” and it consisted of a picture of two dogs, a husky and a yellow Lab, hugging over a fence. At first glance, the author seemed like a normal redditor. The account had been created 11 months earlier, a modestly respectable duration. Every account has a badge that shows its age, and older accounts are rarer and better established. Someone who’s been around is seen as one of us. Because /u/MagnoliaQuezada was many months old, it was able to bypass our subreddit’s homegrown spam filters, living and digital. But on closer inspection, it hadn’t posted a single thing. And now, having seemingly come back to life, it had shown up in my queue.

I could see that /u/MagnoliaQuezada’s user history was blank. And I could see that the hugging-dogs image was kind of blurry. That’s because it had been uploaded and shared and redownloaded so many times. Image quality goes down when photographs are compressed and recompressed by websites as they circulate online. The image had been stolen.

I checked the comments on the post. There was just one, from none other than /u/MagnoliaQuezada:

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Gibberish, perhaps the result of a malfunctioning bot or someone just typing anything to see whether their comments were automatically filtered by our moderation bots. I was now confident I was dealing with a scammer.

From dawn to dusk, scammers—be they bots, trolls, or propagandists—scour the internet searching for pictures or memes that have gone viral in the past: comfort foods, videos of things falling over, puppies. Often puppies. (Cats are also popular tools for the undead, but there are so many cats on the web that it’s tough to know which cats will attract eyeballs.) By sharing puppies, they hope that you will appreciate them, upvote them, and share them, and in so doing lend the zombie account the further appearance of credibility. It’s hard to go wrong with dogs hugging over a fence. It’s tough to accuse someone of being a foreign agent for showing you a pic of a six-week-old Labradoodle.

Had the post gained traction, it would have elevated the user—or bot—behind /u/MagnoliaQuezada, bringing him or her (or it) closer to the 19 million eyes on /r/aww. And that could have made it easier for MagnoliaQuezada to share less obviously lovable things, like links to websites where its owners could say or do whatever they wanted. The corpse might have thrived as a spammer.

But it didn’t, because shortly after its resurrection, /u/MagnoliaQuezada had the misfortune to run into me. I banned her/him/it, muting her/his/its voice. For my 19 million aww subscribers, /u/MagnoliaQuezada never existed. It’s not enough to take away a zombie’s privileges, to warn it to play nice. It’s a zombie. Kill it.

The undead hordes of unused accounts grow larger by the day as Reddit pushes upward toward 400 million active monthly users. Sure, these dormant accounts might be reanimated by their owners—or they might be bought on the gray market on sites like playerup.com or epicnpc.com. Accounts might be hawked as “very active, verified, 25k+ post karma, 225k+ comment karma, 7 gold, natural name, organic only.” A four-year-old account with a few thousand points (or karma, as redditors call it—a score accrued when other people like your posts) can run you hundreds of dollars. You can find YouTube videos telling you how to get started.

I don’t know who /u/MagnoliaQuezada really was, but if I had to guess, I’d say he/she/it was an account farmer—someone trying to gain traction so they could sell the user name. Revisiting the account later, I saw that the posts I’d removed had also been deleted by the owner, erasing the evidence, leaving MQ ready to attempt another fresh start. It’ll have to be on another subreddit, though; with the account quietly banned, no more of its posts will show up on /r/aww.

I ban or mark as spam dozens of these accounts a month, and I’m far from the most active moderator on Reddit. But our queues fill up fast, and sometimes we need to sleep. So zombies probably sneak through as often as we catch them. I’m limited because I go after them account by account, manually noting and checking behavior. Though Reddit supports us and gives us tools to work with, /r/aww’s line of defense mainly comes down to 20 human moderators and three bots. We all do this, pouring in our time, and still things slip by us. One of my co-moderators—I’ll call him Elliot—wanted to do better.

One day last March, Elliot was reading a 2015 article from *The Guardian* about two former employees of an unnamed “troll enterprise” in Saint Petersburg, Russia—the now-famous Internet Research Agency. Elliot is in his mid-thirties, an engineer. He was intrigued by the article’s descriptions of the trolls’ strategies. They’d work in groups to support each other by commenting on and voting for one another’s posts, to simulate popularity in a way that looked real.

It was clever stuff. But to Elliot, a four-year veteran Reddit moderator, it wasn’t that clever. One thing that caught his eye in the *Guardian* article was a detail buried in the 12th paragraph: “The trolls worked in teams of three. The first one would leave a complaint about some problem or other, or simply post a link, then the other two would wade in.” To Elliot, that seemed trackable.

Laptop balanced on the arm of the living room couch, he went to work on a script that would look for groups of users who followed each other around the site and interacted frequently. To find them, his basic script scraped through all the public posts on any page, made a list of people who often replied to one another, and spit the list out into a spreadsheet. The program wasn't all that sophisticated. He didn't really even expect it to work. But then it flashed to life, and at once, Elliot's spreadsheet filled with hundreds of hits. Too many hits. He checked the first result: users arguing about aerosol chemicals in the /r/news subreddit.

The accounts were indeed replying to each other in multiple threads, but they might just be friends—false positives. So Elliot started scanning through his results manually, looking for things that more clearly set off his moderator alarm bells. He looked for anything that seemed Russia-related: discussions of the Syrian civil war, Donald Trump, MAGA, cuck, Hillary Clinton, Pizzagate, Benghazi. For hours, he worked through the list at home and at his office. Finally he had a short list: 46 accounts, all of them behaving in ways the *Guardian* article described.

Elliot was a big deal on Reddit. I brag about my subscriber numbers, but his dwarfed mine. Across his subreddits lived nearly 100 million users, and that kind of power comes with perks—important people listen. Elliot sent CEO Steve Huffman a chat message with his short list, along with a question: Do I have something here?

Huffman forwarded Elliot's list to other staffers. Soon, Elliot was in an email chain with several of them, and he sent links to dozens of suspicious accounts. The excitement Elliot felt at this moment, the nervous anticipation, is something I envy. To a volunteer mod, the chance to catch the enemy in its tracks is a high we're all chasing. We sort through queues of posts, hundreds at a time, getting trolled and insulted and shat on by the internet—for one moment like this one.

Elliot got a reply the next day.

"We appreciate your perspective on this!" wrote Michael Gardner, a Reddit data scientist. "Overall, the activity from these accounts looks like normal activity by frequent commenters."

Elliot hadn't found any Russians, in other words, nor any spammers or bots, according to headquarters. But Elliot wasn't deterred. He kept looking. This time, he changed his methods, looking at one specific subreddit: /r/The_Donald, infamous home of posts such as "THIS IS ON YOU CUCK SCHUMER AND BITCH PELOSI,"

Some of the top mods review more than 10,000 things a month, and apologize when they have to take time off to do their IRL jobs.

ROBERT PECK *(@RobertHPeck) teaches rhetoric at the University of Iowa. He's working on a book about online moderation in the age of fake news.*

with a link to a Breitbart news article about the failed Republican health care bill. Elliot makes no bones about why he went after /r/The_Donald looking for bots: He suspected that if there was Russian activity anywhere, it would be there.

This time, Elliot used his code to track users who shared suspicious domain names on the site, rather than user interaction patterns. Quickly, he found one such domain: geotus.army, which was apparently only ever shared on /r/The_Donald. Clicking it, he found it redirected to usareally.com, a known Russian propaganda site. Elliot checked the user histories of the people sharing the suspicious links. Beyond spreading the links, they were largely inactive. Zombielike.

Elliot was powerful, but he was limited to acting on the subreddits he controlled. He wanted these accounts banned sitewide, so he took this new information to the staff as well, who said they'd look into it.

A few days later, he still hadn't heard from corporate whether they were planning to take action. And this time he felt sure he had found something—something that needed to be made known. Because it didn't seem like the company was doing anything, he wrote up a public post with links to all of the accounts he'd found. He hit publish right before leaving for the gym, on the morning of September 20, 2018.

Twenty minutes later, when Elliot arrived for his workout, he set down his things and checked his phone. There were 127 messages waiting for him. Over the next few days, *Newsweek* wrote about his findings. NBC interviewed him. Reddit banned the domains he'd found, along with a number of the accounts sharing them. He'd actually uncovered an effort to share concealed links to disinformation on the site. And I am still, at minimum, crazy jealous and crazy proud. Because a volunteer did this.

Stories like Elliot's aren't common for Reddit mods, but they aren't unheard of either. Elliot himself cites the influence of several other moderators who uncovered Iranian propaganda on the site, as well as the guidance of spam-hunting expert mods who got him interested in this specific kind of tracking to begin with.

Which is to say: If we sometimes rise to the occasion of, say, fighting propaganda, it's because we're drawing from a deep camaraderie that has developed over thousands of more mundane interactions.

There are plenty of people who think redditors, gamers, internet denizens are people who live in basements. Socially isolated heaps. I am a university lecturer. One of my closest mod friends, /u/mockturne, holds a senior position at a major chain restaurant company. He's also among the cleverest people I know. We argue about which foods are the best. He is always wrong. I am always wrong. We argue over who is more wrong. He ranks sour cream above fruit and says alligator is the best meat.

We go at this for hours. Others join in: They are programmers and engineers for design firms, graduate students studying business, government employees in the UK, parents home from work at night, college kids in their dorms taking a break from Spanish homework, railroad workers laid up with broken legs, waiters and writers and clerks and cooks. Two of my Reddit friends fell in love. My girlfriend and her dad now play videogames with Mockturne, from half a nation away. It often feels as if we can read a digital room better than most people can read a physical one. How do you think we convince redditors to let us run giant forums?

To establish our rules, moderators have staged pure democratic votes, building websites to host them and bots to count the tallies. We build tools for each other that track rule breakers across the site, leaving notes for one another to rely on. Some of the top mods review more than 10,000 things a month, and apologize when they have to take time off to do their IRL jobs. We learn from each other together; we master it together.

At Reddit, all of the volunteers, certainly in the thousands, are trusted with freedom to do as we like with our sections of the site. We appreciate this. I appreciate this. But that isn't why I spend 20 hours a week arguing with people on the internet and banning trolls. I do that because it's satisfying to chase and destroy the zombies, and to do it alongside people I trust. It's fulfilling to be needed and to be skilled. We don't own the site, but we consider its spaces ours.

Among the 127 messages Elliot received when he shared his post about the Russian domains were notes from supporters, swarming his Reddit inbox and private chats, thanking him. But also messages from trolls, death threats. For 12 hours after Elliot went public, the threats kept coming. Upward of 50 of them rolled in by day's end. What felt worse: The Reddit staff chastised him too. "This just makes it much more difficult," CEO Huffman wrote to him, arguing that Elliot's decision to go public got in the way of the staff's investigation into the problem.

As much as we love our volunteer work, Reddit moderators do leave when the work becomes work, when it stops being fun. For Elliot, that time had arrived. That night, he deleted his near-dozen accounts. He passed one of his moderating jobs to another mod. He told us, in back-channel chats, that he was leaving. He also deleted his public posts about his findings. He left one final comment on his way out.

"The admins put forth a genuine effort regarding the domains I alerted them to," he wrote. "They're just not very good at it if a dummy like me using publicly available data can find it before them."

I'd characterize it another way. It isn't that the Reddit staff are bad at their jobs or not trying. (The company says it was already in the midst of a deeper investigation into Russian misinformation.) It's that volunteerism on the web, built around a community of enthusiastic people, is powerful. Elliot was good at his job. Some tech giants pay for this work, building content moderation teams numbering in the thousands. On Reddit, we are close-knit and virtually anonymous.

I think about the cliché "You couldn't pay me to do that." For 20 or so hours a week, the line feels apt. You couldn't pay me to mod reddit.com. Imagine that job: 9 to 5 every day behind a screen, weeding out trolls, totally anonymous yet more vulnerable by the hour for every new racist or sexist you ban. No, I insist on doing it for free.

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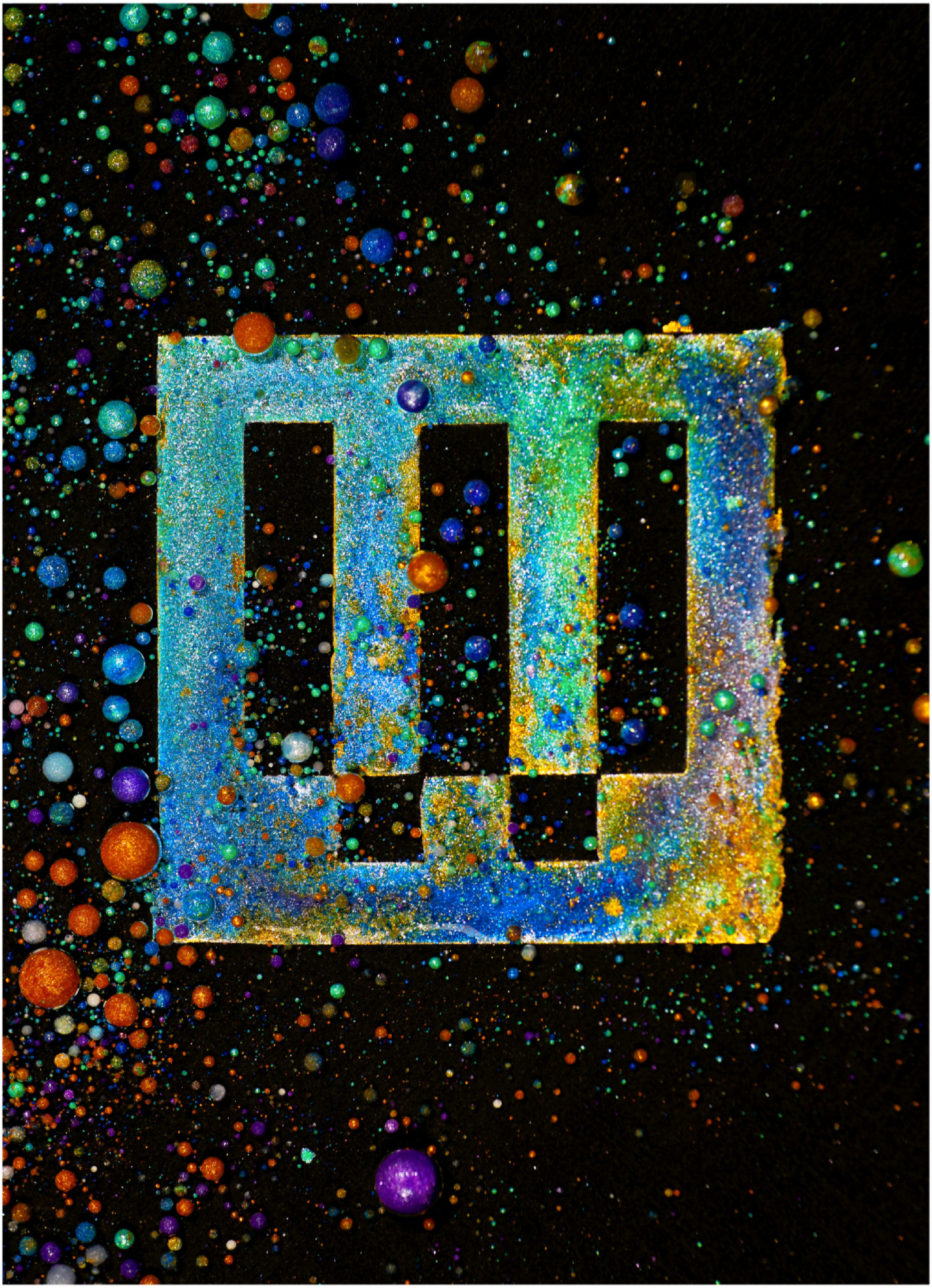
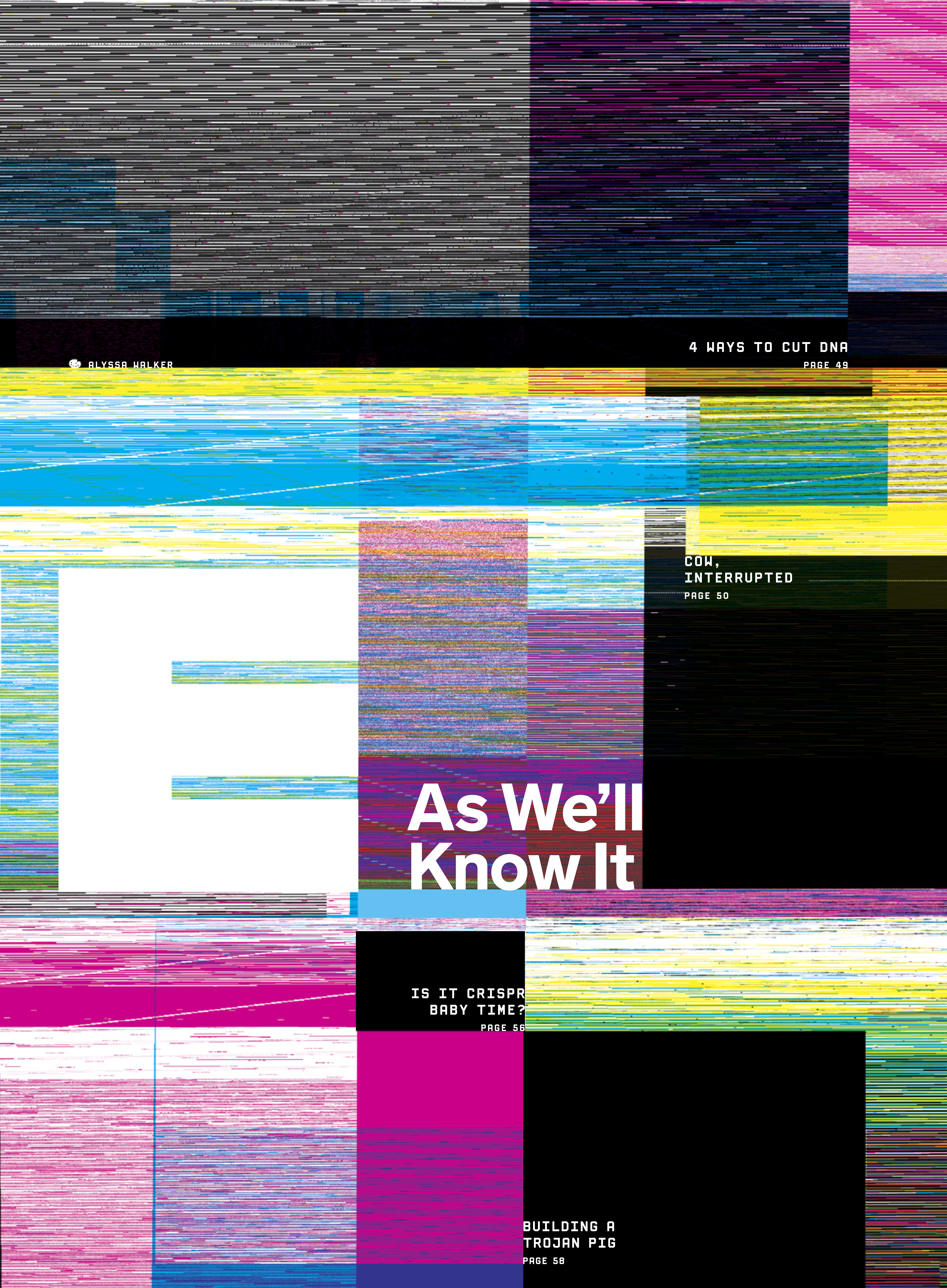


ILLUSTRATION / RUSLAN KHASANOV

HEALTH AND SCIENCE ISSUE

Researchers are ready to unleash cut-and-paste gene editing on the world. But is the world ready?



ALYSSA WALKER

As We'll Know It

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Back in the 1980s, researchers began to notice a strange pattern in the genes of many microbes. There would be a stretch of DNA that read the same forward and backward, then a stretch of what looked like junk, then another palindrome, and so on. No one knew what the segments were for, but they were striking enough that a pair of scientists in Europe dubbed them “clustered regularly interspaced short palindromic repeats,” or Crispr for short.

BY
JENNIFER
KAHN

As it turned out, the mysterious sequences were an immune system. When a microbe was exposed to a new virus, it would cut a swatch of the invader’s DNA (the junk) and store it safely between two dividers (the palindromes). That way, if the virus ever returned, the microbe could simply consult its archive and dispatch the proper immune response.

The task of figuring out the details of that process fell to a later generation of scientists. In 2011, a microbiologist named Emmanuelle Charpentier determined that the Crispr scheme has three key ingredients: an enzyme that acts like a scissors, snipping the strands of the DNA double helix; a guide RNA, which tells the scissors where to cut; and a component that locks the scissors into place. The following year, Charpentier teamed up with biochemist Jennifer Doudna, and the pair asked what proved to be the multibillion-dollar question: Could they exploit this system and use it to edit genes?

The tool they ended up creating—also known, confusingly, as Crispr—not only worked, it effectively blew every existing technology out of the water. To edit a gene using Crispr, all you have to do is give your guide RNA an address corresponding to a particular location on the genome. The scissors will then snip out the selected gene, or even a tiny fragment of the gene, and insert a replacement as needed. (A natural repair mechanism automatically stitches the whole thing back together.)

The result has been transformative. For one thing, Crispr works in almost every animal that scientists have tried, from silkworms to monkeys, and in just about every cell type—kidney cells, heart cells, you name it. (Previous gene-editing techniques even had trouble with *rats*.) What’s more, Crispr is both fast and cheap. Before Doudna and Charpentier made their discovery, it might have taken more than a year to engineer a mouse with a single mutation. Now it can take as little as two days of work. And while the new editing technique sometimes produces typos, it’s far, far more precise than its predecessors. One scientist told me that with Crispr he needs only 10 cells to yield at least one perfect mutation. In the old days, he would have had to fiddle with about a million cells to get the same result.

Scientists around the globe have spent the past seven years honing this new tool,

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JENNIFER KAHN *(@JenniferMKahn) wrote about the nonprofit Ocean Cleanup in issue 26.10.*

using it to study the underlying genetics of disease, speed up drug development, and boost the performance of industrial bacteria and cells. Now they're poised to bring it out of the lab and into the real world. Some of their early applications are already showing promise. Two summers ago, for instance, ExxonMobil announced that it had used Crispr to double the amount of biofuel generated by the marine algae *Nannochloropsis gaditana*. German researchers recently found a way to create Crispr'd pigs that are resistant to African swine fever, a disease that's been ruinous for farmers in sub-Saharan Africa.

But other uses of the technology have been more disturbing. Last November, a Chinese researcher named He Jiankui announced the birth of humanity's first gene-edited babies, twin girls with a Crispr'd version of the CCR5 gene, which he claimed gave them immunity to certain strains of HIV. (The fact that he made his change at the embryo stage means the girls will pass on their edited DNA.) The experiment was widely condemned as unethical, unnecessary, and potentially dangerous; Chinese authorities called it "abominable." But it also augured the next phase of Crispr's development—from a universally embraced lab tool to one with the potential to permanently alter species, ecosystems, and people.

That phase will bring with it a slew of new ethical and regulatory decisions. If we are to find our way through them, we'll need a firm grasp of the facts and an accurate understanding of Crispr's many benefits and risks. But we'll also need to confront a difficult question: How far do we, as individuals and as a society, want this technology to go?

THERE'S MORE THAN ONE WAY TO CUT DNA

Crispr scientists are, essentially, muggers in lab coats. When they need a new pair of DNA-slicing scissors, called a nuclease, they just steal one from a germ. But repurposing microbial machinery isn't so simple: Some nucleases are too big; some are too blunt; some don't work well inside human cells. So, as Crispr wends its way out of the petri dish and into our genes, the search is on for slimmer, sharper tools. With trillions of muggable microbes, there are plenty to choose from. Here are just a few, from the stalwarts to the up-and-comers. —ANTHONY LYDGATE

CAS9 It started with *Streptococcus pyogenes*. Seven years ago, the bug that causes strep throat, toxic shock syndrome, and flesh-eating disease supplied researchers with their first gene-snipping nuclease, Cas9. Though still widely used, Cas9 isn't perfect. For one thing, it's bulky. To get a nuclease to its target gene, you sometimes have to smuggle it across the cell border inside a virus. The larger the nuclease is, the less editing you can squeeze into a single trip. Another problem: *S. pyogenes* has afflicted humans for so long that many of us may carry an immunity to Cas9, making it an iffy editing tool.

CAS12E The US Department of Energy's Joint Genome Institute maintains a database of microbial DNA from various unsavory places, including a Superfund site in California and a shuttered uranium mill in Colorado. A couple of years ago, after poring through 155 million gene sequences, scientists found three previously undiscovered nucleases, including one they called CasX. Now renamed Cas12e, it has a couple of things going for it: It's tiny, which makes it easy to deliver into a cell, and it doesn't appear to be related to Cas9, which makes it less likely to trigger the same immune response in humans.

CAS12B If you give a mouse fermented shrimp compost, you get *Bacillus hisashii*, a heat-loving gut bacterium with a nuclease called Cas12b. (Other microbes produce the same enzyme, but their versions don't work well at human body temperature.) Earlier this year, in the journal *Nature*, researchers reported they'd created a streamlined version of Cas12b that's especially well suited to editing human immune cells. Best of all, their lab-grown mutant is about 20 percent smaller than that first Cas9 and way less prone to off-target snipping.

CAS12A This handy little nuclease is smaller and more accurate than Cas9, and it has shown promise in speeding up the production of biofuels and bioplastics. Last year, researchers announced that Cas12a can also screen for HPV in STD swabs. First they programmed it to seek out two cancer-causing strains of the virus. Then, in a test tube, they combined it with a kind of fluorescent alarm system. When the nuclease came into contact with HPV, it would hack apart both the virus and the alarm compound, causing the test tube to light up. Voilà, a positive result.

CHRISTIE
HEMM KLOK

Horn-free?
Yup.
Heat-tolerant?
Sure.
Flu-proof?
Of course.

COW, INTERRUPTED

BY
GREGORY BARBER

Crispr could make our food supply more efficient and more humane. But it's struggling to get out of the lab and onto our plates.

Alison Van Eenennaam at the UC Davis Beef Barn.

HOPES WERE RUNNING HIGH FOR COW 401, and cow 401 serenely bore the weight of expectations. She entered the cattle chute obligingly, and as the vet searched her uterus, making full use of the plastic glove that covered his arm up to his shoulder, she uttered nary a moo. A week ago, Cow 401 and four other members of her experimental herd at UC Davis were in the early stages of pregnancy. But now, following a string of disappointing checkups, it was all down to her. Alison Van Eenennaam, the animal geneticist in charge of the proceedings, kept watch from off to one side, galoshes firmly planted in the damp manure, eyes fixed on a portable ultrasound monitor. After a few moments, the vet delivered his fifth and final diagnosis. "She's not pregnant," he said. Van Eenennaam looked up. "Ah, shit," she muttered.

Cow 401 and her herdmates were the product of two and a half years of research, Van Eenennaam's attempt to create a strain of gene-edited cattle specially suited to the needs of the beef industry. Had everything gone as planned, all the calves in this experiment would have been born male—physiologically, at least. Like humans, cattle carry two sex chromosomes; those born XX are female, and those born XY are male. But it isn't the Y that makes the man. It's a single gene, called SRY, that briefly flickers to life as an embryo grows and instructs it to develop male traits. Using Crispr, Van Eenennaam's team added a copy of SRY to the X chromosome too. That way, even if a cow was born genetically female, she'd be expected to appear male all the same. Since beef ranchers generally prefer males to females (more meat for the money), Van Eenennaam believed there could someday be a market for these Crispr'd animals.

More than that, though, the project was a proof of concept. One of Van Eenennaam's goals is to make the raising of livestock not only more efficient but also more humane. If a calf's sex could be altered with a copy-paste of a single gene, that might pave the way for all kinds of experimentation—and not only in the beef business. Although ranchers may prefer male animals, their colleagues in the egg and dairy industries favor females. Since bulls can't make milk and roosters can't lay eggs, it's cheaper to destroy them than raise them to adulthood. But if you could ensure that only heifers and hens are born, the carnage wouldn't be necessary.

GREGORY BARBER *(@GregoryJBarber), a* WIRED *staff writer, wrote about selling his personal data on the blockchain in issue 27.01.*

The Davis team wasn't yet sure what had gone wrong with the pregnancies. They'd done their work with such care. First they located a target area on the bovine genome and created a custom set of Crispr scissors to cut the DNA and insert the new gene. Then they took a trip down the interstate to a slaughterhouse in Fresno, where they purchased a fresh batch of ovaries. Back in the lab, they aspirated the eggs, fertilized them, and set their Crispr scissors loose. They let the resulting embryos grow for a week, biopsied them to make sure the edits had gone as planned, then froze them until the cows were ready for implanting.

Perhaps, Van Eenennaam thought, the arduous process had simply knocked the life out of the embryos. "Science is a bitch," she said with a shrug. But there was a more troubling possibility—an issue with the gene edit itself. On a map of the bovine X chromosome, the location where they'd inserted SRY seemed to be within a stretch of extraneous code, far from any life-critical genes. But then again, the map they currently had was about as accurate as a 16th-century atlas of the New World, full of unknown and mislabeled territories. Maybe, by tinkering in the wrong place, they had arrested development in the womb.

TWENTY-FIVE YEARS AGO, VAN Eenennaam was a student at Davis in the early days of the GMO craze. Animal scientists, long limited by the pace of traditional trial and error breeding, could now mix and match genetic traits from different organisms, giving their livestock strange new powers. At Davis, for instance, they engineered a line of goats that carried a human protein called lysozyme in their milk. (Later on, researchers realized that, when fed to children in the developing world, that milk could prevent diarrhea.) As a young faculty member at Davis in the mid-2000s, Van Eenennaam explored a method for modifying cows to produce milk with extra omega-3s. Then, just as she prepared to begin experiments in actual cattle, she says, the money dried up.

Around that time, the Food and Drug Administration had decided to classify genetic modifications to food animals as veterinary drugs. At specific issue were transgenes—DNA ported from one species into another—which, in the agency's view, altered "the structure or function" of the animal. This meant that scientists would have to submit to an expensive approval process before anything reached the grocery store. There were calls for reform, but policymakers lacked the will to implement regulatory changes that would both promote research and assuage people's growing fears about GMOs. With no path to commercialization in sight, and with the looming threat of a public backlash, the institutions that had funded the work ended their support. Only one animal from that period, the AquAdvantage Salmon, has since been approved for human consumption, though no one in the US is eating it yet, owing to regulatory hand-wringing over how it should be labeled. The lysozyme goats still amble, idly, around a pasture on the Davis campus.

Van Eenennaam argues that Crispr experiments like hers—those not involving transgenes—should be treated differently. As she sees it, the technology is just a faster, more precise version of what farmers have done for centuries, because it makes changes that could have occurred in the organism on their own. The US Department of Agriculture, which oversees gene editing in plants, appears to share this view; in March 2018, it decided, in most cases, to regulate this use of Crispr like it does traditional breeding methods. But the most recent guidance from the FDA, issued in January 2017, seems to lump gene editing in with the old GMO techniques. That's because, as the agency sees it, both approaches present similar risks, not only to people but also to animal welfare—something the USDA doesn't have to consider. Van Eenennaam worries that the same fears and heel-dragging as before could scuttle the field before it has a chance. "The engineering debate killed my career," she says. "Now this editing debate has the potential to kill my students' careers."

For all the anxiety and ambiguity surrounding Crispr, there's little doubt that it could revolutionize farming as Van Eenennaam hopes. In January, British researchers announced plans to raise chickens with an immunity to influenza. A small genomic incision, they hypothesized, could prevent the virus from infecting its hosts. That would not only save chickens from untimely demise but also cut out a likely conduit for a devastating human pandemic. You may not like the idea of Crispr meddling with grandma's chicken pot pie recipe, but would you relent if it could stop the next Spanish flu?

"I'd hope so," says Randall Prather, a geneticist at the University of Missouri. His lab has raised pigs that are resistant to porcine reproductive and respiratory syndrome, or PRRS, an untreatable disease that costs the US swine industry more than half a billion dollars each year. The solution, he says, comes down to modifying as few as two DNA base pairs out of 3 billion. Prather licensed the technology to a British company called Genus, which says it expects to spend tens of millions of dollars on the FDA approval process.

Yet not all Crispr experiments in livestock offer such unambiguous benefits. Many merely aim to improve efficiency, speeding up the process that gave us broiler chickens four times the size they were in Eisenhower's day. That fuels perceptions that gene editing will only encourage the worst inclinations of factory farming. In Brazil, for example, scientists recently bred Angus cattle that carry a heat-tolerance gene called Slick. While this could eventually be a path to readying the global cattle industry for climate change, for now it likely means that the Brazilian Amazon will have to support even more cows than it already does.

Robbie Barbero, who led efforts to modernize biotech regulations in the Obama White House, says that it's time for the FDA to offer some clarity. "In the absence of a regulatory path that's rational and easy to understand, it will be almost impossible for any animals to make it to market," he says. With transgenes, he argues, it was possible to wrap your head around the logic of regulating changes as drugs. "But when you're talking about regulating changes to the genome that could've happened naturally, you're asking to stretch the imagination," he says. The draft guidance, Barbero notes, was intended as a starting point, not the final word.

If and when the FDA decides to weigh in, says Hank Greely, a bioethicist and professor of law at Stanford, it will have to reckon with the unique risks of gene editing—that an edit might produce new allergens, for example, or spread from livestock to their wild cousins. His underlying fear, however, is "the democratizing nature of Crispr." An argument against GMOs was that the expense of creating them would consolidate power in the hands of wealthy multinationals; a company such as Monsanto would spend millions engineering a new transgenic crop, then sell it to struggling farmers at an exorbitant price. But the remarkable ease of gene editing, Greely says, could have the opposite effect. It could push certain rogue actors—say, "a guy with a dog kennel or a biologically sophisticated rancher"—toward cavalier, DIY experimentation. That's why Greely thinks researchers should be required to register their edits.

For now, though, political momentum appears once again to have stalled. That's left nascent projects, like Van Eenennaam's, waiting for answers.

IF THERE IS A PURGATORY FOR GENE-edited cattle, it can be found in the Davis Beef Barn, which is home to six young penitents. About five years ago, their father, a bull, was genetically dehorned by a Minnesota-based company called Recombinetics. Just as egg farmers prefer hens, dairy farmers prefer polled, or hornless, cows. Often they'll prevent the horns from growing by burning them off with a hot iron or applying caustic chemicals. So, using a Crispr-like technology known as Talens, Recombinetics gave the bull two copies of the polled variation, in the hope that none of his descendants would have to undergo the procedure.

Five of those hornless descendants turned out to be male, which meant they wouldn't be much use to the dairy industry anyway. Van Eenennaam has asked the FDA for permission to sell them as food. "They're either all going to be incinerated or they're all going to become steaks," she explains. One of the bulls gently sniffs her fingers through the wooden slats of the pen. "Sorry to talk about this in front of you guys."

Princess, the lone polled female, is hanging out a few pens away. Before she and her brothers can be introduced into the food supply, the FDA requires that they pass a range of tests, both genetic and physical. Their gene-edited uncle supplied the meat for quality testing; now Princess will be bred so that, when her milk comes in, it can be analyzed. But Van Eenennaam says the agency hasn't told her clearly what results it is looking for, almost as though it's searching for the risks it wants to regulate. For instance, the FDA asked her to confirm, via full genome sequencing, that there had been no unintended edits that jeopardized the animals' safety. But sequencing the same genome 20 times over, as Van Eenennaam did, will turn up slightly different results with each pass. And besides, she says, even if you could pinpoint any errant edits, what would they tell you about the animal's health? She advocates a wait-and-see approach: "There's a natural evaluation process called 'living' that will weed out anything that's weird." (The FDA does not comment on pending applications.)

Even as Van Eenennaam and her calves are hung up in regulatory limbo, she is looking ahead to the next step in the process: scaling up genetic improvements on the ranch. Unlike pigs and chickens, whose reproduction is strictly controlled, beef cattle tend to procreate unsupervised, out on vast grazing ranges. This makes it hard to ensure that desirable traits, like swift growth or well-marbled meat, get passed down. Van Eenennaam thinks she's found a solution. She plans to take a group of bulls, knock out the gene that allows them to create sperm, and swap in a replacement from a superior animal—perhaps even one that carries the edits for hornlessness or all-male offspring. The result would be ordinary bulls with, as Van Eenennaam puts it, "excellent balls." Rather than spreading their own mediocre genes, they'd spread the elite genes of others—and they'd do it faster than ranchers could manage on their own.

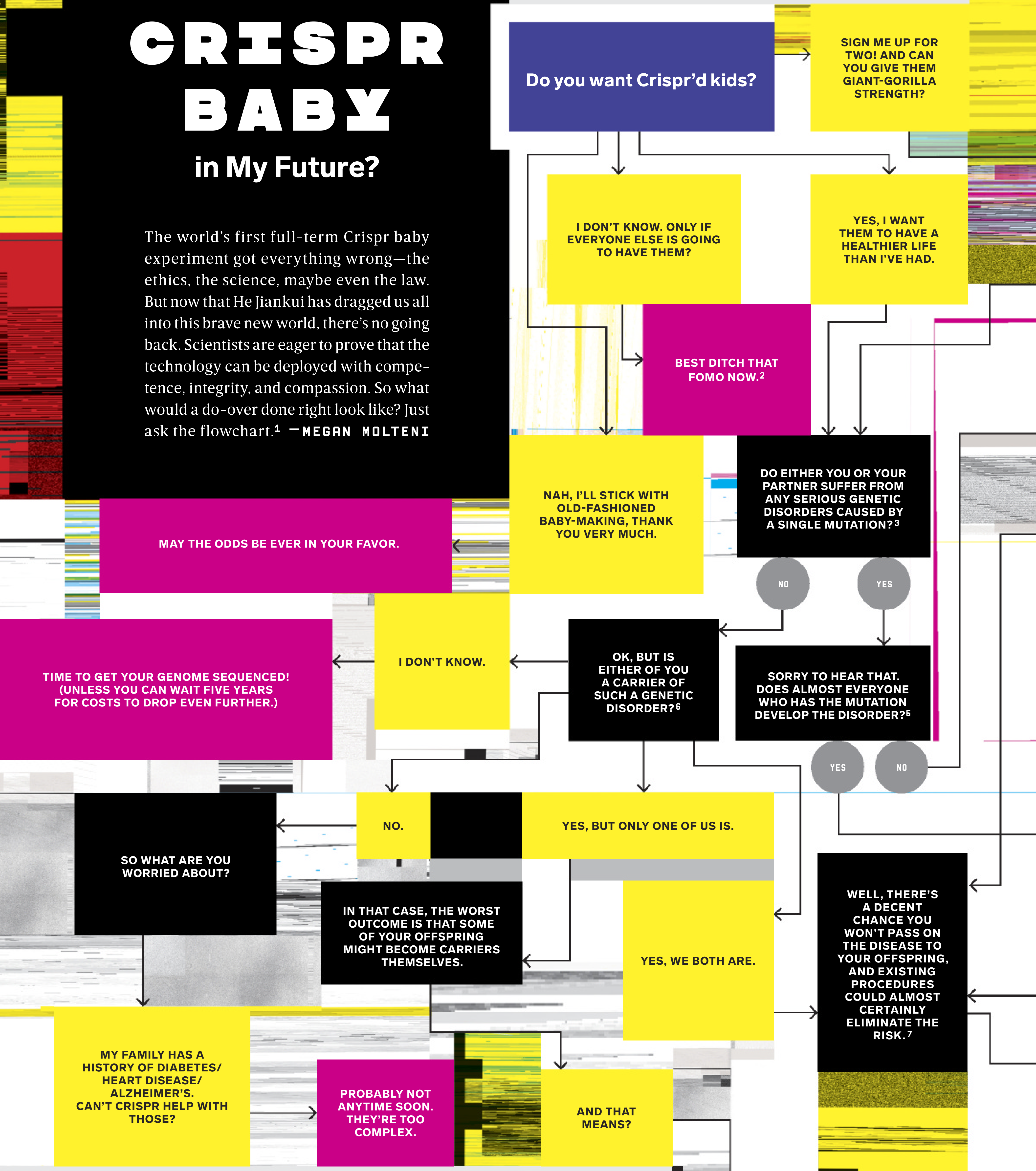
Van Eenennaam and her colleagues are also focused on getting their earlier experiment working. After the disappointment of the pregnancy checks, they soon came up with two possible explanations for what went wrong: Either they inserted the SRY gene in the wrong place or they damaged the embryos in the lab—perhaps during the biopsy, when they were checking to see whether the edit took. In the next stage of the project, they'll investigate both possibilities at once. First, they will insert SRY into a completely different chromosome, at a location where other researchers have successfully dabbled in mice. But this edit will be different from the last one: It will include a gene, borrowed from a jellyfish, for red fluorescence. If the insertion is successful, the cells will simply glow, no biopsy required.

It's not an ideal solution. If all goes well, Van Eenennaam won't have gene-edited cattle, as she originally intended; she'll have a transgenic herd. So while she'd hoped to get the FDA's blessing to sell the animals at the end of her research, she now plans to incinerate them instead. Even the mothers, which naturally share small amounts of genetic material with their offspring, could be considered tainted. "I've been resisting putting a transgene in," she says. "But we're just going to have to bite the bullet and kill them and their mothers and everything that touches them."

Van Eenennaam does the math: $15,000 to buy 10 cows from a local rancher, plus $8 a day, each, to pasture them until a Christmas birth. Her grant will have ended by then, and she worries she won't get another one.

Is There a CRISPR BABY in My Future?

The world's first full-term Crispr baby experiment got everything wrong—the ethics, the science, maybe even the law. But now that He Jiankui has dragged us all into this brave new world, there's no going back. Scientists are eager to prove that the technology can be deployed with competence, integrity, and compassion. So what would a do-over done right look like? Just ask the flowchart.[1] —**MEGAN MOLTENI**



Do you want Crispr'd kids?

SIGN ME UP FOR TWO! AND CAN YOU GIVE THEM GIANT-GORILLA STRENGTH?

I DON'T KNOW. ONLY IF EVERYONE ELSE IS GOING TO HAVE THEM?

YES, I WANT THEM TO HAVE A HEALTHIER LIFE THAN I'VE HAD.

BEST DITCH THAT FOMO NOW.[2]

NAH, I'LL STICK WITH OLD-FASHIONED BABY-MAKING, THANK YOU VERY MUCH.

MAY THE ODDS BE EVER IN YOUR FAVOR.

DO EITHER YOU OR YOUR PARTNER SUFFER FROM ANY SERIOUS GENETIC DISORDERS CAUSED BY A SINGLE MUTATION?[3]

NO

YES

OK, BUT IS EITHER OF YOU A CARRIER OF SUCH A GENETIC DISORDER?[6]

SORRY TO HEAR THAT. DOES ALMOST EVERYONE WHO HAS THE MUTATION DEVELOP THE DISORDER?[5]

YES

NO

I DON'T KNOW.

TIME TO GET YOUR GENOME SEQUENCED! (UNLESS YOU CAN WAIT FIVE YEARS FOR COSTS TO DROP EVEN FURTHER.)

NO.

YES, BUT ONLY ONE OF US IS.

SO WHAT ARE YOU WORRIED ABOUT?

IN THAT CASE, THE WORST OUTCOME IS THAT SOME OF YOUR OFFSPRING MIGHT BECOME CARRIERS THEMSELVES.

YES, WE BOTH ARE.

WELL, THERE'S A DECENT CHANCE YOU WON'T PASS ON THE DISEASE TO YOUR OFFSPRING, AND EXISTING PROCEDURES COULD ALMOST CERTAINLY ELIMINATE THE RISK.[7]

MY FAMILY HAS A HISTORY OF DIABETES/ HEART DISEASE/ ALZHEIMER'S. CAN'T CRISPR HELP WITH THOSE?

PROBABLY NOT ANYTIME SOON. THEY'RE TOO COMPLEX.

AND THAT MEANS?

---

[1] This chart should not be construed as medical advice or used for family-planning purposes. Please consult your doctor and/or a genetic counselor.

[2] Making a Crispr baby requires in-vitro fertilization. Today, less than 1 percent of babies worldwide are conceived using IVF.

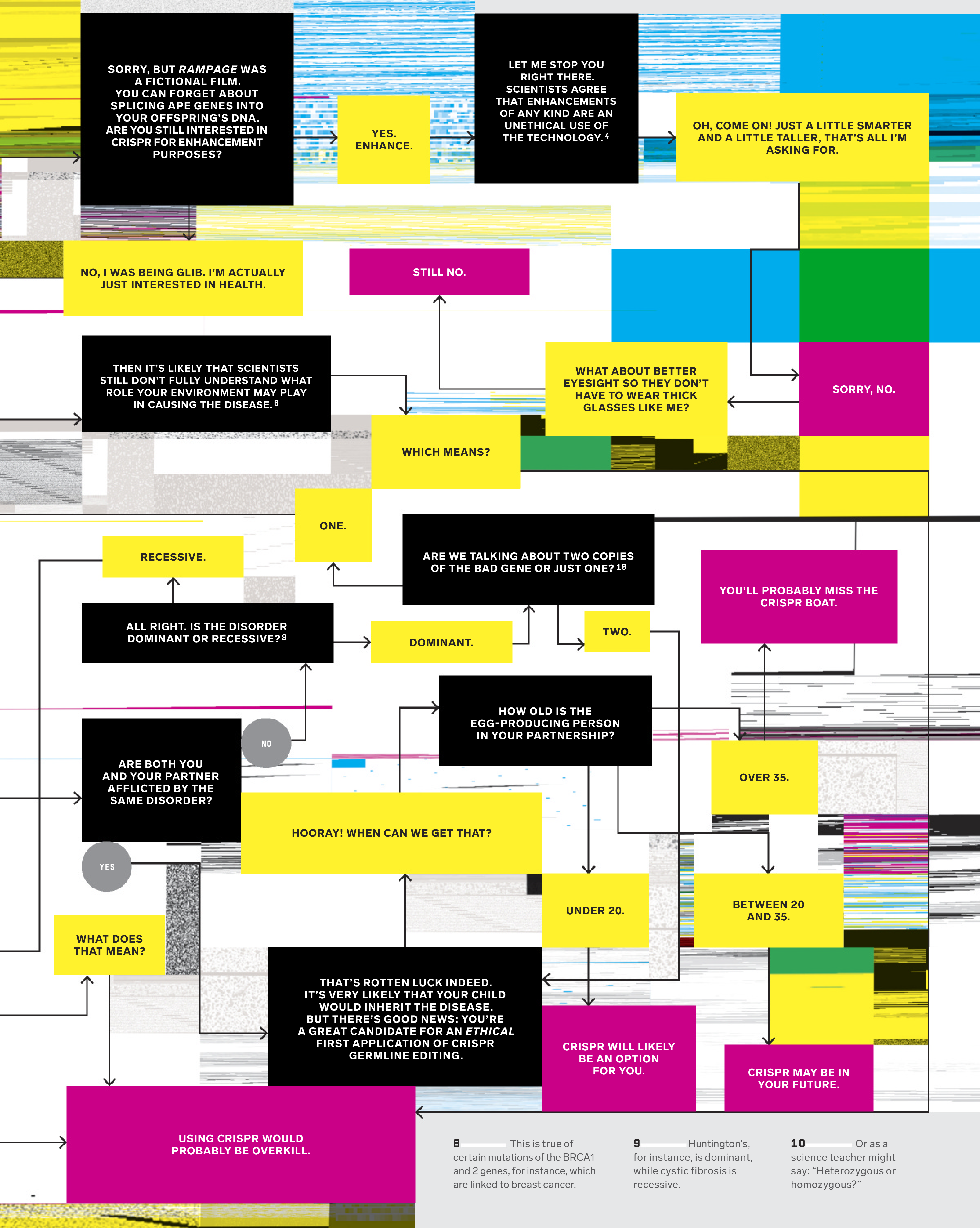
[5] In other words, is it what a geneticist would call highly penetrant?

[6] Carriers have just one copy of the mutation, so they usually don't get the condition themselves.

[7] Doctors can sample DNA from IVF embryos, screen them for any genetic diseases, and start pregnancies only with the unaffected ones.

[3] Scientists have identified about 10,000 such diseases in humans, including sickle-cell anemia and cystic fibrosis. They occur in roughly 1 in 100 births.

[4] But not all of them agree on precisely where the line between disease eradication and enhancement falls.



SORRY, BUT *RAMPAGE* WAS A FICTIONAL FILM. YOU CAN FORGET ABOUT SPLICING APE GENES INTO YOUR OFFSPRING'S DNA. ARE YOU STILL INTERESTED IN CRISPR FOR ENHANCEMENT PURPOSES?

YES. ENHANCE.

LET ME STOP YOU RIGHT THERE. SCIENTISTS AGREE THAT ENHANCEMENTS OF ANY KIND ARE AN UNETHICAL USE OF THE TECHNOLOGY.[4]

OH, COME ON! JUST A LITTLE SMARTER AND A LITTLE TALLER, THAT'S ALL I'M ASKING FOR.

NO, I WAS BEING GLIB. I'M ACTUALLY JUST INTERESTED IN HEALTH.

STILL NO.

SORRY, NO.

WHAT ABOUT BETTER EYESIGHT SO THEY DON'T HAVE TO WEAR THICK GLASSES LIKE ME?

THEN IT'S LIKELY THAT SCIENTISTS STILL DON'T FULLY UNDERSTAND WHAT ROLE YOUR ENVIRONMENT MAY PLAY IN CAUSING THE DISEASE.[8]

WHICH MEANS?

ONE.

ARE WE TALKING ABOUT TWO COPIES OF THE BAD GENE OR JUST ONE?[10]

YOU'LL PROBABLY MISS THE CRISPR BOAT.

RECESSIVE.

ALL RIGHT. IS THE DISORDER DOMINANT OR RECESSIVE?[9]

DOMINANT.

TWO.

HOW OLD IS THE EGG-PRODUCING PERSON IN YOUR PARTNERSHIP?

ARE BOTH YOU AND YOUR PARTNER AFFLICTED BY THE SAME DISORDER?

NO

YES

OVER 35.

HOORAY! WHEN CAN WE GET THAT?

WHAT DOES THAT MEAN?

UNDER 20.

BETWEEN 20 AND 35.

THAT'S ROTTEN LUCK INDEED. IT'S VERY LIKELY THAT YOUR CHILD WOULD INHERIT THE DISEASE. BUT THERE'S GOOD NEWS: YOU'RE A GREAT CANDIDATE FOR AN *ETHICAL* FIRST APPLICATION OF CRISPR GERMLINE EDITING.

CRISPR WILL LIKELY BE AN OPTION FOR YOU.

CRISPR MAY BE IN YOUR FUTURE.

USING CRISPR WOULD PROBABLY BE OVERKILL.

[8] This is true of certain mutations of the BRCA1 and 2 genes, for instance, which are linked to breast cancer.

[9] Huntington's, for instance, is dominant, while cystic fibrosis is recessive.

[10] Or as a science teacher might say: "Heterozygous or homozygous?"

Juan Carlos Izpisua Belmonte wants to use Crispr to grow human organs in livestock.

BUILDING A TROJAN PIG

BY ERIKA HAYASAKI

What could go wrong?

TO THE ANCIENT GREEKS, THE CHIMERA WAS a ferocious creature—part lion, part goat, and part snake. The first chimera that Juan Carlos Izpisua Belmonte ever created, in 1992, was considerably less intimidating: It consisted of an embryonic mouse limb grafted onto the wing of an embryonic chicken.

Belmonte was a young scientist at the time, working in a lab in Heidelberg, Germany. He was transfixed by the mysteries of gene expression—the biological signals that govern how an animal develops—and the pure potential that lurked in embryonic cells. Take any vertebrate: a chicken, a pig, a human. At maturity, they are dramatically different organisms, but they start out nearly identical. Belmonte began to wonder: If a mouse limb could live on a chicken's

CHRISTIE HEMM KLOK

wing, what else might be possible? How else might scientists alter the signals that dictate what a creature becomes?

Belmonte's interest in the malleability of destiny was, on some level, personal. The child of poor, barely educated parents in rural southern Spain, he had been forced to drop out of school for a few years as a young boy to support his family with farmwork. Only as a teenager did he return to the classroom—at which point he promptly set off on a rapid trajectory from philosophy (Nietzsche and Schopenhauer were favorites) to pharmacology to genetics.

By 2012, Belmonte was one of the world's preeminent biologists, running his own lab at the Salk Institute in La Jolla, California, and another one in his native Spain. Like his colleagues all over the globe, he was pondering how to make use of a powerful new tool in the discipline's arsenal—the Crispr-Cas9 gene-editing platform. After the first major Crispr papers appeared, Belmonte quickly set his sights on an audacious target. In the US alone, around 100,000 people are on a waiting list for an organ transplant at any given time, and some 8,000 of them die each year for lack of a donor. As Belmonte saw it, Crispr and chimeras could be a solution. He hoped to use the new gene-editing technique to fool the bodies of large livestock into becoming incubators for human hearts, kidneys, livers, and lungs.

Belmonte's exploratory research started in mice. Using Crispr, he and his team deleted the genes that allowed the animals to grow several organs, including eyes, a heart, or a pancreas. Rather than let these maimed mouse embryos develop on their own, the Salk researchers injected some rat stem cells into the mix. Lo and behold, the rat cells replaced the missing organs, and the animals lived a normal murine lifespan. By 2017, Belmonte and his colleagues had moved onto bigger test subjects. They injected human stem cells into 1,500 ordinary pig embryos, then implanted those embryos into sows. Within about 20 days, some had developed into people-pig chimeras. It was a modest success. The embryos were far more pig than person, with approximately one human cell for every 100,000 porcine cells. But the experiment was nonetheless a major milestone: They were the first chimeric embryos ever created by merging two large, distantly related species.

Opposite: Belmonte's lab at the Salk Institute in La Jolla, California.

→

ERIKA HAYASAKI
(@ErikaHayasaki) wrote about a scientific effort to dial down human pain in issue 25.05.

Much as he did with mice and rats, Belmonte plans to use Crispr to switch off a pig's propensity to create its own organs, then fill the gap with human cells. But the second step—getting the human cells to take root in pigs at higher rates—has proved devilishly hard. "The mouse-rat efficiency is quite good," Belmonte says. "Human-pig efficiency is not so high. So that is a problem." Today, Belmonte's lab is slogging through an arduous process of trial and error, testing how different animal and human cells interact when combined, in hopes that they can apply what they learn to pig-human chimeras. But even that slog is, by the research standards of just a few years ago, proceeding at lightning speed. With conventional methods, Belmonte says, "it would take hundreds of years. But thanks to Crispr, we can move quickly to many, many genes and modify them."

If Crispr has helped to supercharge the ambition of Belmonte's work, it has also sent him careening into some of the thorniest ethical terrain in science. The ancients regarded chimeras as bad omens, and modern Americans have been similarly spooked by them—especially those that blur the line between human and animal. In his 2006 State of the Union address, President George W. Bush ranked the creation of such hybrids as among "the most egregious abuses of medical research." In 2015, Belmonte learned that he was in the running for a Pioneer Award, one of the National Institutes of Health's most prestigious and generous grants; then he found out that his application was on hold, he says, because of his chimera work. That same year, the NIH suspended federal funding for any studies that introduce human stem cells into animal embryos, saying it needed time to think through the ethical issues. A year later, the agency announced plans to lift the moratorium and opened the idea to public comment; 22,000 responses flooded in. So far, funding is still on pause. (Belmonte eventually won a Pioneer Award, but still carried out much of his pig research in Spain with private funds.)

John De Vos, director of the department of cell and tissue engineering at Montpellier University Hospital and Medical School in France, has no trouble envisioning worst-case scenarios involving pig chimeras. If too many human cells make it into a pig's brain, for instance, the animal could theoretically develop new kinds of awareness and intelligence. (In 2013, scientists in Rochester, New York, injected mice with human brain cells, and the mice turned out smarter than their peers.) "It would be horrible to imagine a form of human consciousness locked in the body of an animal," De Vos says. What if scientists inadvertently created a pig able to intellectualize its own suffering, one with a sense of moral injustice? Even if you could accept killing a farm animal to harvest its organs—which many animal welfare activists don't—surely it would be monstrous to kill one with humanlike intelligence to go along with its humanlike pancreas.

Belmonte offers a straightforward solution to this problem: more Crispr. Using gene editing, he says, researchers can prevent a human cell from colonizing the brain of a pig. Similar interventions could keep human DNA from entering the porcine germ line—proliferating into future piglet-people for generations to come—another scenario that has made bioethicists especially squeamish. "In the laboratory," Belmonte says, "we have technologies that could avoid those ethical concerns."

A wiry 58-year-old, Belmonte has a dimpled smile, narrow eyes, and a gentle but

energetic demeanor. Chimera research is, as it happens, only one major front that his lab is exploring with Crispr. He and his team have also performed a slew of experiments in epigenetic editing—a variation on Crispr that modulates gene expression rather than hack away at the DNA sequence itself. With it, they have reversed the symptoms of diabetes, kidney disease, and muscular dystrophy in mice. For good measure, they're also trying to rewind the aging process itself.

"He is pushing boundaries on the things we can do nowadays," says Pablo Juan Ross, a professor in the department of animal science at UC Davis, who has been conducting chimera experiments with pigs and sheep in his own laboratory. Both scientists are keen on proving the value of gene editing and chimeras. With such a dire need for human organs, Ross asks, wouldn't we rather have technology that can develop them on demand with animals, instead of waiting for the next teenager to die in a car accident?

But while he is eager to show what might be possible, Belmonte is not particularly impatient to see his research leave the laboratory. He opted to destroy his fetal pig chimeras during their first trimester, before they could develop into anything more ethically confounding—despite the fact that in Spain, where they were grown, regulations would have allowed Belmonte to euthanize the animals after bringing them to term. And he is altogether wary of editing genes in people. "We need to know much more before we can use Crispr in a human being," Belmonte says. "I wouldn't dare to move it outside of the lab yet."

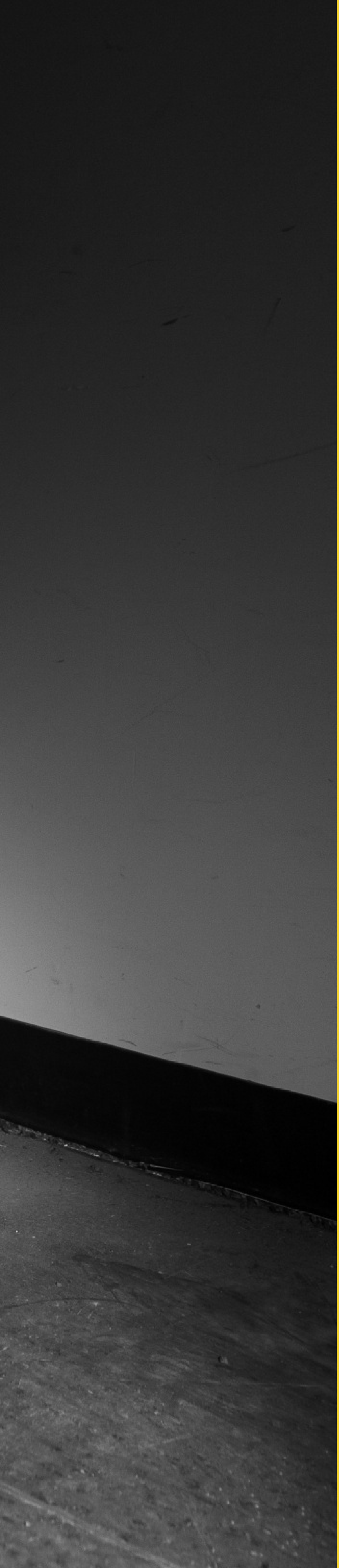
The science itself isn't the only thing that needs to progress. There also has to be a thorough debate about gene editing, Belmonte says; scientists like him must have a strong voice in it, but so should physicians, the public, and the government. De Vos agrees. "Einstein did basic research in physics," he says. "But it was at a country level that it was decided to apply these findings to bomb Hiroshima—not at the scientist level."

Still, the clock is ticking on that debate. Belmonte firmly believes that scientists today are on the cusp of curing diseases, reversing aging, and saving lives with homegrown organs. "What we are talking about is not like taking an aspirin," he says. "It could change our own evolution, our own species."

A revolution in the culture at large—or at least a reckoning—will lag not far behind, whether we like it or not. "We change our values depending on the facts that are presented to us," Belmonte adds. "That's the way societies have evolved." Given the pace of new developments in biology, we already have a lot of catching up to do.

_HEALTH
AND SCIENCE
ISSUE_

A POX ON US ALL



SYNTHETIC BIOLOGY IS MAKING IT EASIER THAN EVER TO PRODUCE LIFE-SAVING VACCINES—

AND LIFE-TAKING VIRUSES THAT HUMANITY IS NOT PREPARED TO FIGHT.

by David Kushner
Photographs by Sinead Kennedy

AT AROUND 11:30 AM ON JULY 1, 2014, A SCIENTIST FROM THE FOOD AND DRUG ADMINISTRATION WENT INSIDE ROOM 3C16, A COLD-STORAGE AREA AT THE NATIONAL INSTITUTES OF HEALTH LABS IN BETHESDA, MARYLAND.

THE FDA HAD BEEN using the space since the early 1990s to store samples for biological research but had been cleaning it out in preparation for a move to a nearby campus in Silver Spring.

The scientist who entered saw 12 mysterious cardboard boxes on a crowded shelf in the far left corner of the storage space and pried one open to see what it contained. Inside, dozens of long vials were packed in rolls of white cotton and sealed with melted glass; many of the labels were worn to the point of illegibility. The scientist noticed one vessel that held some loose, freeze-dried material. Its label bore a single decipherable word: “variola,” another word for smallpox—a disease that the 19th-century British historian Thomas Babington Macaulay deemed “the most terrible of all the ministers of death.”

The highly contagious virus spreads through close contact, bodily fluids, or contaminated objects. It starts like chicken pox: The victim runs a high fever and is prone to vomiting. A rash develops in the mouth and spreads quickly over the entire body, like tiny marbles pushing up from under the skin. Some 30 percent of people who contract the virus die within two weeks. Those who survive are often scarred, blinded, or disfigured.

Smallpox ravaged the world for centuries. It wasn’t until 1796 that English physician Edward Jenner famously discovered how to turn the immune system against the disease. Even so, it took centuries for the vaccine he created to be fully deployed. Smallpox killed an estimated 500 million people in the 19th and 20th centuries before it was finally eradicated worldwide in 1980. Yet here in this cluttered Maryland lab were six forgotten vials of the dreaded poxvirus, including at least two live samples still capable of growing and infecting untold masses.

During a two-year investigation into the origin of the vials, the FDA determined that they dated to February 10, 1954. But the agency couldn’t figure out how or why they ended up in a cold-storage room at the NIH. The incident triggered a government-wide search for other dangerous materials that may have been overlooked and led to revisions in the FDA’s policies on the storage of infectious agents. The 60-year-old smallpox strains were destroyed under the watch of World Health Organization officials.

The existence of the vials raised another chilling possibility: Could smallpox make a comeback? If these samples were left behind, who knows how many others could remain. The US maintains enough of the smallpox vaccine to protect all 328 million Americans. But in the decades since the disease was eradicated, scientists have discovered that several groups of people—those with HIV, pregnant women, newborns, and cancer survivors among them—are at risk for complications from the vaccine, such as heart inflammation and brain infections. It’s likely that most of these people would be advised to avoid taking the remedy, as would anyone sharing a home with them. Given those significant limitations, many health officials and researchers believe there’s a pressing need for a better smallpox vaccine.

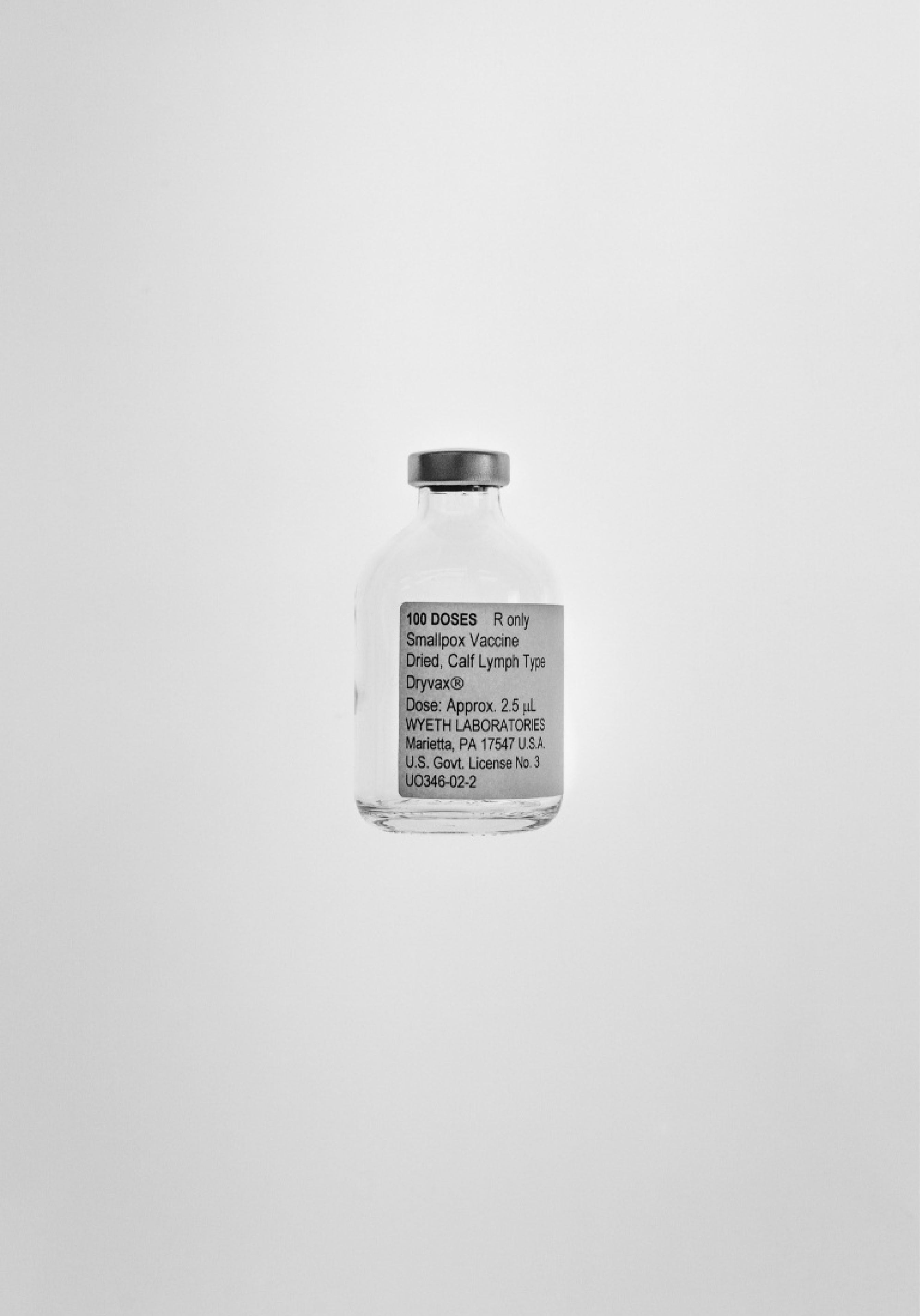
It’s this mission that possesses David Evans, a veteran virologist at the University of Alberta in Canada. The son of a medical health officer in what was the British colony Northern Rhodesia (now Zambia), Evans has been studying poxviruses for more than 30 years.

As one of the world’s foremost experts on smallpox, Evans believes it’s only a matter of time before the disease—or one of its ugly cousins in the pox family—could resurface, brought to life by a hostile government, a terrorist, or an amateur biohacker using gene editing and commercially available DNA fragments.

If that occurs, he says, the world needs to be ready with the safest, most efficient vaccine possible. The best way to improve upon a vaccine is to make one derived from the virus itself.

So two years ago, in a Hail Mary attempt to defend against potential bioengineered viruses, Evans and his research associate did something unthinkable: They revived an extinct cousin of smallpox called horsepox, using mail-order DNA.

The objects in the photographs are representations, not the actual objects discussed in the story.



The Frankensteinian act stirred outrage among the international scientific community, which cast Evans as the Walter White of synthetic biology. Despite the fury he provoked, Evans has no regrets. Better he be the first to resurrect these deadly specters, the virologist maintains, than someone with nefarious intentions. “Nothing will stop the state actor or technically sophisticated country that decides to want to do this,” Evans adds, so better to be prepared.

W

WHEN SMALLPOX WAS ELIMINATED nearly 40 years ago, after millions of people were given the vaccine in Africa, Asia, and South America, it was hailed as one of the greatest achievements in human history. In a grim act of Cold War diplomacy, the last two smallpox samples were stored for future study at the Centers for Disease Control and Prevention in Atlanta and at the State Research Center of Virology and Biotechnology in Siberia. Ever since, the World Health Organization has kept tabs on the samples to ensure they are safe.

In 2001, Evans joined the WHO’s scientific advisory committee on smallpox. The aim for many in the group was for Russia and the US to destroy those final samples of smallpox for good. “The hope and expectation,” Evans says, “was that the committee would say, ‘Yep, we’re all done, they’ve dealt with all these research goals. You can close it down and autoclave the viruses.’ ”

The following year, however, an experiment by scientists at the State University of New York at Stony Brook suggested that simply destroying the samples might not be enough. On July 11, 2002, the researchers revealed that they had synthesized the polio virus, which had been wiped out in the US in 1979. It was the first time a virus had been created from scratch with synthetic DNA. The work was funded by the Pentagon in part to establish whether terrorists could pull off such a feat. The answer was yes. It took the SUNY researchers three years to cobble the virus together using mail-order DNA and genetic sequences referenced from an online public database. The experiment’s surprise success raised the possibility of a cyberpunk-style era of biowarfare, and the possibility that an exponentially deadlier disease, smallpox, could be cooked up in a lab through the science of synthetic biology.

For Evans, the study proved that no virus could truly be considered extinct. “I said, ‘Yeah, well, there’s the writing on the wall for people concerned with eradicating smallpox,’ ” he recalls. After polio’s revival, he was one of the first to warn the WHO about the potential resurrection of smallpox. But his warnings fell on deaf ears. Though Evans comes across as a measured scientist, his frustrations were mounting. He felt like Chicken Little and feared that action wouldn’t be taken until it was too late. “You know the way the world works,” he tells me. “It focuses on crises, right? It wasn’t a crisis.” At least not yet.

O

ON A CRISP FALL day in September in Edmonton, Evans sits behind the desk of his cluttered office at the University of Alberta wearing a blue button-down shirt and khakis. He has wispy gray hair and small, round glasses. There's a large microscope on his windowsill and shelves weighed down by thick books about viruses. Two stickers on his computer capture his natural skepticism—one reads "Really?" and the other "WTF?" ("I'm suspicious of reporters," he tells me within the first few minutes of our meeting.)

Buying samples of synthetic DNA is surprisingly easy. The trade is overseen by the International Gene Synthesis Consortium, an industry-led group that works with government agencies to screen orders and buyers. But such oversight can't prevent someone from purchasing hazardous DNA samples on the black market. A cursory search online brings up dozens of sources for samples from China, Germany, and beyond. China "is kind of notorious for having unregulated pharmaceutical companies, right?" Evans says. Chinese biohackers could "be quite capable of running an unregulated DNA synthesis company."

In June 2015, thanks in part to research by Evans and his colleagues into synthetic biology, public health advisers issued a report warning of smallpox's potential return. "With the increasing availability of DNA fragments that can be synthesized from simple chemicals, it would be possible to re-create variola virus," the report found, "and that could be done by a skilled laboratory technician or by undergraduate students working with viruses in a relatively simple laboratory."

The following year, the US national intelligence director at the time, James Clapper, cited bioengineered pandemics as one of his agencies' biggest concerns; the *Worldwide Threat Assessment* report added genome editing to its appraisal of current weapons of mass destruction and proliferation—alongside North Korea's nukes, Syria's chemical weapons, and Russia's cruise missiles. As Bill Gates warned in 2017 at the Munich Security Conference, "the next epidemic could originate on the screen of a terrorist intent on using genetic engineering to create a synthetic version of the smallpox virus."

If that wasn't enough, a disturbing mystery emerged out of Russia. The *Siberian Times* reported in early 2017 that professor Ilya Drozdov, the 63-year-old microbiologist who ran the state research facility where Russia's sole smallpox sample is held, vanished from his hometown of Saratov in southwestern Russia. No further information has been made public. A WHO spokeswoman said it was not in the organization's "mandate to confirm or deny the existence of an investigation."

F

FOR YEARS, EVANS had been urging his colleagues to upgrade their smallpox defenses. But it wasn't until he met Seth Lederman that he found a like-minded scientist with the will and resources to do something about it. The CEO and cofounder of a New York company called Tonix Pharmaceuticals, Lederman was interested in funding research to develop biodefense technologies and drugs.

Lederman shared Evans' apprehension about the potential for a smallpox epidemic. "There's an urgent need for a new vaccine," he says. Smallpox vaccinations ended in 1978, meaning that the roughly 5 billion people worldwide under the age of 40 have not been inoculated.

Lederman, a former associate professor of medicine at Columbia University, was prepared to commit

↑

DAVID EVANS RAISED ALARMS ABOUT THE POSSIBILITY OF REVIVING POXVIRUSES—AND THEN REVIVED ONE HIMSELF.

his company to coming up with a solution. He was convinced that the secret to a better vaccine could be found in horsepox, a lesser-known cousin of smallpox. Horsepox isn't known to be harmful to humans, but its genetic makeup is closely related to smallpox. In theory, the closer one can get to a virus's origins, the more effective the vaccine that can be derived.

Evans was intrigued. But the Centers for Disease Control maintains a single sample of horsepox, extracted from an infected horse in Mongolia in 1976, and Evans said it was unlikely he would be able to use the sample for commercial purposes. There was another option for getting their hands on some horsepox, Evans told Lederman: They could re-create the virus from scratch using synthetic DNA, similar to the way researchers had synthesized polio a decade earlier. The horsepox genome sequence had been published by researchers in 2006, offering up a road map for the virus's revival.

Evans didn't know if he could succeed. Despite his Cassandra warnings, no one had ever engineered a virus in the smallpox family. Lederman decided the attempt was worth the gamble. He offered Evans' lab $200,000 to try to bring horsepox back to life.

When I ask Evans if he had any doubts about re-creating a cousin of smallpox, he hesitates. "You do think about that," he says, "I don't like controversy." He had seen what had happened when polio was synthesized and had spoken with those researchers. Evans accepted that many would not agree with his choice. But he also believed, emphatically, that people already knew how to create such a virus—it was just that no one had achieved it yet. This was his chance, then, to prove that a synthetic version of a poxvirus was not only conceivable but a looming reality. "As long as people kept debating whether it was possible," Evans notes, "nothing was ever going to be done about it." It was time to put those questions to rest.

In 2016, with approval from the University of Alberta's biosafety office, Evans purchased 10 DNA fragments from GeneArt, a DNA synthesis company based in Regensburg, Germany. The synthetic DNA, which arrived by FedEx as vaporized powder, was harmless. "If you wanted to, you could eat it," Evans says, "My guess is that it would have a fizzy tang, like Pop Rocks."

The arduous job of assembling the horsepox genome fell to Evans' research associate, a young microbiologist named Ryan Noyce. Noyce wears his dark hair short and favors socks that read "Get shit done." Like Evans, he has devoted his career to studying the nuances of viruses.

Building a virus from scratch is like assembling Lego blocks. A decade ago, Evans had improved on a process that uses a "helper virus"—another form of a poxvirus—to kick-start the replication of DNA. In this case, once the helper virus started growing inside a cell, Noyce would use pipettes to introduce a solution containing the horsepox DNA. "You're laying down a piece here, a piece here," Evans says, "mortaring them together." The fragments affix to each other using an enzyme called DNA ligase, which acts as a kind of glue. If the DNA fragments are introduced into a cell in the right way, under just the right conditions, they'll join together through a natural biological process and hopefully grow into a virus.

Noyce had to get every step of the process exactly right, from the sequence of the fragments to the timing of their insertion into the cell. If any part of the chain fails, the entire process falls apart. "It takes a tremendous amount of planning and timing and design work," Evans explains.

Every weekday morning at 7:30, Noyce crossed the University of Alberta campus to reach Evans' dimly lit lab. He'd don his long white lab coat, then spend 10 hours moving between his computer and a microscope, stitching DNA fragments together based on horsepox's previously published genome sequence.

One day, after 18 months of meticulous work in the lab, Noyce looked through his microscope and saw it: a clearing of cells infected with the horsepox virus. He'd successfully re-created a poxvirus. But the rush of excitement was quickly tempered by the realization of what of was to come. Noyce believed that if they could help develop better vaccines, that "would outweigh the potential negatives" of reviving a pox. But given the history of the virus, Evans says, "We knew that there was going to be controversy."

SYNTHETIC BIOWEAPONS, A REALITY CHECK

How worried should we be about warring countries or terrorists turning synthetic viruses, bacteria, and microbes into bioweapons? For some doomsday scenarios—the creation of, say, a wholly manufactured monster mashup of bad viruses—the answer is not very. But there is still plenty to freak out about. Last year, the US Department of Defense commissioned a report from biosecurity and synthetic biology experts to assess the threats. Here are some of their most urgent warnings.
—SARASWATI RATHOD

CONCERN LEVEL

🔴 = HIGHEST
🟠 = HIGH
🟡 = MEDIUM

🔴 MICROBIOME INTERLOPERS

Microorganisms inhabit our guts, mouths, and skin and help us in many ways. A rogue microbe slipped into the mix could, in theory, cause our good bugs to produce harmful chemicals. In practice, this would be really hard to do, but the novelty of this technique put it on the list of top concerns.

🟠 MUTATED VIRUSES

Introducing mutations into a virus's genome almost always leads to a gentler form of the bug. That's how a vaccine for measles was created. But scary stuff could also be made. In 2014, researchers found that just five mutations could transform an avian flu into an airborne virus—making it far more likely to spread (at least among ferrets).

🔴 REVIVED VIRUSES

A bioterrorist, armed with basic lab equipment and online databases filled with genetic blueprints for deadly viruses, could conceivably re-create a fatal disease like smallpox or the Spanish flu. Illnesses with relatively small genomes, like polio, are easier to resurrect than more genetically complex diseases like smallpox or herpes.

🔴 SOUPED-UP BACTERIA

Because their genomes are more stable, bacteria tend to be easier to modify than viruses. While you might not be able to get the building blocks for a deadly pathogen (like the one that causes anthrax) from a mail-order genetics company, you could modify a more benign bacterium to make it resistant to antibiotics or able to produce more toxins.

🟡 MODIFIED IMMUNE SYSTEMS

It might be possible to develop and deliver a specially engineered virus or chemical capable of suppressing the body's defenses or turning them against it. However, the human immune system is highly complex, and we still don't fully understand it, making manipulation difficult.

The trio published their findings in the scientific journal *PLOS One* in January 2018—and the blowback was swift and brutal. Critics accused Evans and Noyce of opening a Pandora's box that could send humanity back to the dark ages of disease. *The Washington Post*'s editorial board wrote that "the study could give terrorists or rogue states a recipe to reconstitute the smallpox virus." Tom Inglesby, director of the Center for Health Security at the Johns Hopkins Bloomberg School of Public Health, denounced the research on National Public Radio: "Anything that lowers the bar for creating smallpox in the world is a dangerous path." Gregory Koblentz, director of the biodefense program at George Mason University, warned in the journal *Health Security* that the synthesis of horsepox "takes the world one step closer to the reemergence of smallpox as a threat to global health security."

The *PLOS One* paper also triggered calls for tighter regulation. Elizabeth Cameron, vice president of global biological policy and programs for the Nuclear Threat Initiative, a nonprofit that works to prevent attacks by weapons of mass destruction, issued an ominous warning that "the capability to create and modify biological agents is outpacing governmental oversight and public debate."

Evans still bristles over the criticism, which he feels missed the point. "One of the very irritating things on the reporting on our work was the idea that somehow it was so easy," he says. "No it's not. Ryan busted butt to make this." For now, synthesizing a virus, as Evans and Noyce have, requires a high level of expertise. But while such a feat may be difficult to achieve, even Evans admits that "you make it more accessible to people simply by letting them know it can be done."

T

THE RESEARCH PAPER SEEMED to spur the federal government to shore up its defenses against the threat that someone could create and unleash a synthetic virus. In June, the US National Academies of Sciences, Engineering, and Medicine released a 231-page study warning that even existing viruses like the common flu could be tweaked in a lab to evade immune responses and resist therapeutics (see sidebar). Several efforts are now underway to better assess potential threats before it's too late.

Darpa has launched an initiative called Safe Genes to protect service members from the accidental or intentional misuse of genome-editing technologies. The agency is trying to develop military tools to both counter and reverse the effects of synthetically created bioweapons. The Office of the Director of National Intelligence has announced its own initiative to find better methods for detecting and evaluating synthetic bioweapons. The system is designed to prevent rogue actors from getting their hands on the building blocks needed to make a dangerous virus.

To make better screening tools, the government enlisted Ginkgo Bioworks, a biotech startup founded by a group of MIT PhDs. Based in an old Army warehouse along Boston Harbor, Ginkgo's main business is making custom microbes for use in everything from sustainable agriculture to perfumes. But with its government contracts, the biotech company helped build an algorithm that can recognize any genetic sequence on the "threat list" of potentially harmful viruses and bacteria. The software—a literal antivirus program—would be voluntarily installed on the servers of every company that synthesizes DNA. It's like a wanted list for genetic riffraff. "If somebody tries to synthesize horsepox, alarm bells go off," says Patrick Boyle, Ginkgo's 34-year-old head of codebase. At that point, the DNA company can ask questions of the buyer and, if warranted, deny the sale.

Of course, even these automated checks can't prevent determined buyers from obtaining samples through less scrupulous vendors on the black market. As with computer viruses, new strains appear from the ether before society is aware they exist. The same is true for trying to keep ahead of potentially lethal synthetic DNA.

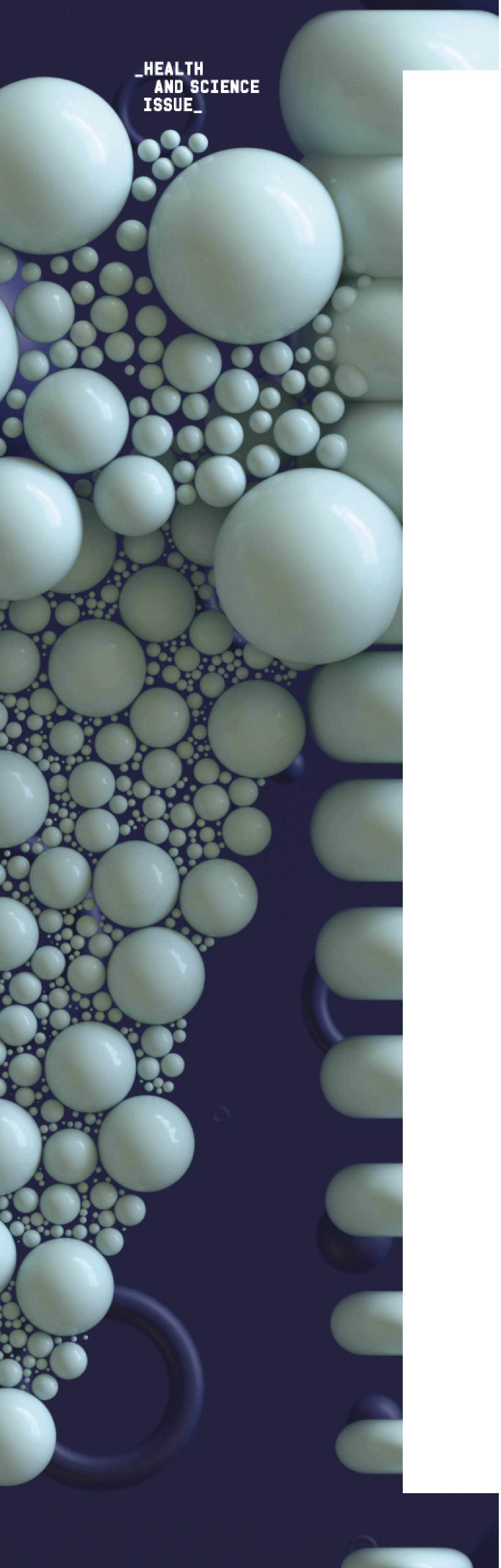
The scientists at Ginkgo never expected to be policing the DNA trade. But as tools like Crispr allow for cheaper and easier creation of new biological organisms, technology is quickly surpassing enforcement measures. In 20 years, Boyle predicts, it will be possible to synthesize smallpox from home. He likens this moment to the early days of computing, when the concept of computer viruses was still new: "If I was working for the US government, I would have wanted to fund an effort in antivirus software in 1975," he says. "That's exactly the thinking we're doing now," but with synthetic biological viruses.

At this uncertain juncture, synthetic biology is entering new territory. It's only a matter of time before others with the skill and wherewithal follow Evans and Noyce's lead and replicate other viruses. Although not all viruses are deadly, scientists and bioengineers are in a race to predict and defend against new threats. There's no telling when a manufactured disease will become a reality. If that occurs, the culprit might be a lab-trained terrorist or a basement biohacker, a bumbling grad student or a Russian microbiologist on the lam.

In the meantime, Evans and Noyce's horsepox work is now the basis of a new smallpox vaccine called TNX-801. It's being developed by Tonix, the pharmaceutical firm that funded their research. In a study published last year, the vaccine was shown to successfully protect mice from a relative of smallpox.

Today, Evans and Noyce are using what they learned in the horsepox effort to try to use DNA fragments to engineer oncolytic viruses, which target and destroy cancer cells. Past the lab where they work, down a quiet hallway and inside a windowless room, a beige freezer hums at –79 degrees Celsius. Inside, the synthetic horsepox samples remain under lock and key.

DAVID KUSHNER *(@davidkushner) is the author, most recently, of* The Players Ball: A Genius, a Con Man, and the Secret History of the Internet's Rise.



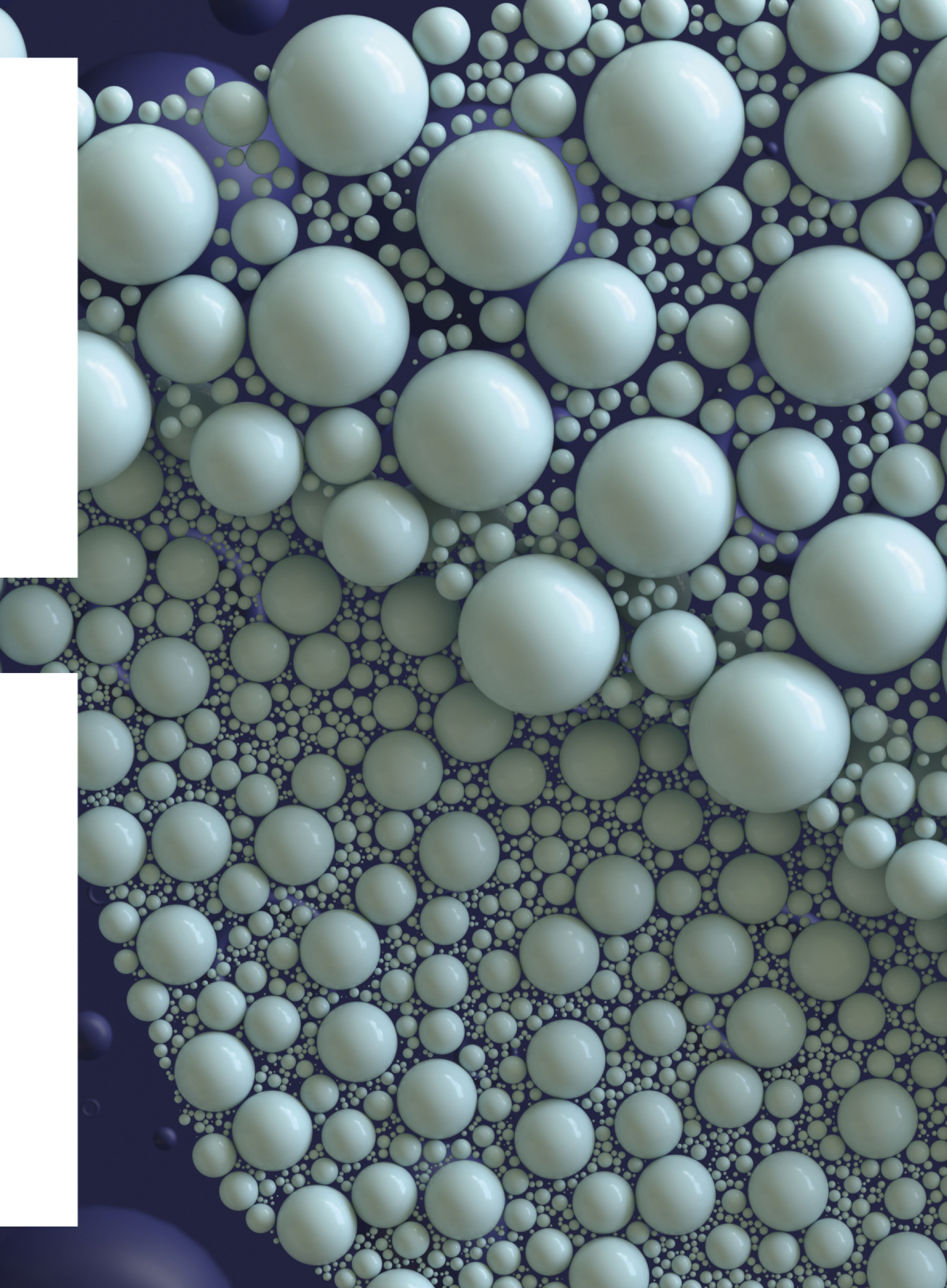
Most advanced-stage cancers mutate, resisting drugs meant to kill them.

Now doctors are trying to harness the principles of evolution—and thwart that lethal adaptation.

The Darwin Treatment

By
Roxanne
Khamsi

Art
Hayden
Zezula



In October 1854, a government entomologist was inspecting some farmland outside the town of Ottawa, in northern Illinois, when he came upon a disturbing scene in a cabbage patch.

The large outer leaves of the vegetables were "literally riddled with holes, more than half their substance being eaten away." With each step he took around the ravaged cabbages, tiny swarms of little ash-gray moths rose from the ground and flitted away. This was, it appears, the first record in the United States of the diamondback moth, an invasive pest that in its larval form shows a fondness for cruciferous vegetables. By the late 1800s the moths were chewing through the leaves of cabbages, brussels sprouts, collards, and kale from Florida to Colorado.

To fight this invasion, farmers started bombarding their fields with primitive pesticides. This worked. Or seemed to. It killed most of the moths, but those that survived the poison reproduced, and the population bounced back stronger than ever. For decades, one pesticide after another failed as the moths evolved to withstand it. Even the grievously toxic DDT was no match for the diamondback. Beginning in the late 1950s, agriculture experts started to abandon the idea of eradication and adopted a new strategy. Farmers would leave the moths alone until their numbers exceeded a certain threshold, and only then would they deploy pesticides. Remarkably, this helped. The moths did not die out, but the pest could be managed and crop damage held in check.

When Robert Gatenby heard this history of the diamondback moth in 2008, he immediately latched onto it. Gatenby is not a farmer nor an agronomist nor a fan of cruciferous vegetables—in fact, he deeply loathes brussels sprouts. He is a radiologist by training and heads the radiology department at the H. Lee Moffitt Cancer Center in Tampa, Florida. But unlike your typical doctor, he is also obsessed with the evolutionary principles put forth more than 150 years ago by Charles Darwin. The story of the diamondback moth appealed to Gatenby as a useful metaphor for his own project—one concerned not with crops but with cancer.

Like the diamondback moth, cancer cells develop resistance to the powerful chemicals deployed to destroy them. Even if cancer therapies kill most of the cells they target, a small subset can survive, largely thanks to genetic changes that render them resistant. In advanced-stage cancer, it's generally a matter of when, not if, the pugnacious surviving cells will become an unstoppable force. Gatenby thought this deadly outcome might be prevented. His idea was to expose a tumor to medication intermittently, rather than in a constant assault, thereby reducing the pressure on its cells to evolve resistance.

Just as ecologists allow for a manageable population of diamondback moths to exist, Gatenby's method would permit cancer to remain in the body as long as it doesn't spread further. To test this idea, Gatenby got permission in 2014 to run a trial on advanced-stage prostate cancer patients at Moffitt. The patients had cancer that no longer responded to treatment; their drug-resistant cells were winning an evolutionary battle within the body, surviving an onslaught of toxic drugs where weaker cancerous cells had succumbed. The hope was that, by using a precise drug-dosing scheme developed using evolutionary principles, they could slow the rise of the mutations that would endow some cancer cells with the fitness to survive. Gatenby's name for the approach was adaptive therapy.

One of the patients in the trial was Robert Butler, a British oil-exploration engineer who had retired in Tampa. In 2007 he was diagnosed with prostate cancer, and seven years later, after taking the drug Lupron and getting blasts of radiation, his prostate tumor had progressed to stage 4, advanced cancer. Butler did not give up, though. He tried a newly approved immunotherapy treatment—one that involved having cells from his blood sent by courier to a facility outside Atlanta, where they were mixed with a molecule that activates immune cells, and then shipped back to Florida to be injected back into him. The treatment was expensive—its sticker price can be as high as $120,000—but the threat that the cancer would progress remained.

When Butler and his wife showed up at his oncologist's office at the Moffitt Cancer Center in August 2014, they braced for what would come next; they had heard about invasive treatments, like radioactive seed implants. So they were intrigued when the doctor told them about Gatenby's trial and asked if Butler wanted to participate. He would take a powerful and exceedingly expensive drug called Zytiga, but not in the scorched-earth, kill-all-the-cells fashion that is standard. Instead he would receive only as much Zytiga as was necessary to stop the cancer from growing. The idea was radical and counterintuitive. His last best shot at escaping death from his cancer was to give up on curing it.

Knowing the modified Zytiga regimen wasn't designed to rid him of cancer left Butler, the engineer, with a question about how the doctors would measure the success of their new treatment approach. He asked, "How do we know this stuff is working?" And one of his doctors replied, "Well, you won't be dead."

I

In the United States we use military metaphors when we talk about cancer. We battle and we fight, and if we survive, we're victorious. The attitude traces back in part to 1969, when the Citizens Committee for the Conquest of Cancer ran an ad in *The Washington Post* and *The New York Times* imploring the president with the words "Mr. Nixon: You can cure cancer." The call to action helped trigger the country's "war on cancer" with a determination that, using enough medical weaponry, the malignant foe could be obliterated.

By the mid-1970s, however, signs were beginning to emerge that certain strategies aimed at total eradication were liable to backfire. Against this backdrop, a cancer researcher named Peter Nowell published a seminal paper in *Science* in 1976. Nowell conjectured that evolutionary forces drive certain cell populations in tumors to become progressively more malignant over time. The cells inside a tumor are in competition, not only with nearby healthy cells, Nowell argued, but also with each other. Nowell suggested—and later research confirmed—that certain DNA alterations grant cancer cells resistance against chemotherapy or other treatments, causing them to edge out drug-sensitive cells through a process of natural selection.

Nowell conveyed his ideas to his students at the University of Pennsylvania School of Medicine, sometimes smoking a cigarette as he lectured. His theories were respected but slow to catch on. He emphasized that tumors may become deadlier as they accumulate more genetic errors. It was an idea ahead of its time. Scientists back then didn't have the technical capability to measure all the changes in the vast genomes of tumor cells. Instead, they could sequence only little tidbits of DNA at a time, and most scientists viewed cancers as the fruit of just a few genetic mutations.

One of the medical students listening to Nowell lecture in the late 1970s happened to be a young Bob Gatenby. But Nowell's ideas didn't make a strong impression on him, Gatenby says; instead, what inspired him was what he witnessed in his first years as a practicing radiologist on the bloody front lines of the war on cancer.

By the mid-1980s, Gatenby had secured a job at the Fox Chase Cancer Center in Philadelphia. At that hospital and others around the country, clinical trials were putting breast cancer patients through an extreme treatment: a combination of a potentially lethal dose of chemotherapy followed by a bone marrow transplant. The treatment was harrowing. The women had diarrhea and nausea, and some had so much lung damage they had difficulty breathing. Others experienced liver damage and weakened immune systems that left them vulnerable to serious infections. As a radiologist, Gatenby's job was to interpret x-rays and other scans of the patients, and he saw the treatment failing. Out of more than 30,000 women with breast cancer in the US who underwent the procedure between 1985 and 1998, as many as 15 percent died from the treatment itself. "What happened was these women suffered horribly, and they weren't cured," Gatenby says.

Around the same time as the breast cancer trials, the father of a colleague of Gatenby's came to the hospital to receive an initial, aggressive round of chemotherapy for lung cancer. According to the colleague, her father arrived on a Friday with no apparent symptoms and was dead by Monday. "That event to me was very traumatizing," Gatenby recalls, and the cause to him seemed obvious. "I couldn't understand why you would treat someone with a fatal disease and kill them with your therapy. It just didn't feel right to me." During this fraught period, Gatenby's own father died from esophageal cancer.

Gatenby felt there must be a better way to treat cancer—to outsmart it rather than carpet-bomb it. He had studied physics in college and believed that biologists could leverage equations to capture the forces driving cancer the same way physicists use math to describe phenomena like gravity. Whereas Nowell had put forth general theories about how cancers followed evolutionary principles, Gatenby was taking a further leap: He wanted to figure out a way to describe the evolution of cancers with mathematical formulas.

B

By 1989, Bob Gatenby was preoccupied with modeling the evolution of cancers. During the day he would scrutinize the x-rays of cancer patients, and at night, after he and his wife had put their young kids to bed, he would sit at the kitchen table in their suburban Philadelphia home and pore over medical journals. The patterns he started seeing in the literature led him to a question: What if cancer cells outcompete normal, healthy cells in the body in the same way an animal species edges out its competitors in nature?

Gatenby recalled that ecologists had come up with equations to describe the balance between predators and prey. As an undergraduate at Princeton University, he had learned the classic example of the math that plotted how growing populations of snowshoe hares fuel the rise of the lynx that feed on them. He began dusting off old books and buying new ones to educate himself on species interactions.

For a year Gatenby read and mulled. Then, in 1990, on a family trip to the Atlantic coast of Georgia, he found himself stuck in a hotel room one afternoon with his two napping children. Out of nowhere, an idea presented itself. He grabbed a pad of hotel stationery and a pen and began scribbling down some key formulas from population ecology. Those formulas, called Lotka-Volterra equations, have been used since the 1920s to model predator-prey interactions and, later, competition dynamics between species, and were among the ones he had recently brushed up on at home. Gatenby thought this set of formulas could also describe how tumor cells compete with healthy cells for energy resources such as the glucose that fuels them.

When he returned to Philadelphia, he spent what time he could at a typewriter composing a paper that laid out this theoretical model. As soon as he finished, he showed it to some colleagues. He didn't get the response he had hoped for: They thought it was ridiculous to try to use ecological equations to model cancer. "To say that they hated it would not do justice to how negative they were about it," he says. His peers thought that a brief set of formulas couldn't capture cancer's seemingly infinite complexities.

Louis Weiner, who worked alongside Gatenby at the time, recalls that their colleagues viewed Gatenby's ideas as offbeat. "Treatment orthodoxy at that time favored high-intensity, dose-dense treatments aiming to eradicate every last tumor cell in a cancer patient," says Weiner, who is now director of the Georgetown Lombardi Comprehensive Cancer Center in Washington, DC. "Bob's perspective was antithetical to those beliefs."

But Gatenby pressed on and succeeded in getting the paper, chock-full of Lotka-Volterra equations, accepted in the prominent journal *Cancer Research* in 1991.

Despite the publication of his theory, he still couldn't convince oncologists that his idea had practical merit. "I think that they felt intimidated," Gatenby says. "Most physicians are mathematically illiterate." He found that the medical establishment was reluctant to publish much of his follow-up work.

In the years afterward, Gatenby moved up the ladder to lead the department of diagnostic imaging at Fox Chase Cancer Center. He was later appointed head of the department of radiology at the University of Arizona College of Medicine in Tucson, and he continued to garner recognition for his skilled interpretation of scans and to receive federal grants to study cancer.

Then, in 2007, the Moffitt Cancer Center offered Gatenby a job as chair of the radiology department. He had a condition: He would come if the hospital created a division where he could pursue in earnest the link between Darwin's principles and cancer. The Integrated Mathematical Oncology Department, born from this negotiation, is the first math department in a cancer hospital, he says. Finally, Gatenby had a place where he could put his ideas to the test.

G

Gatenby arrives at his corner office at Moffitt most days by 7 am. He's 67 now, and his hair is gray at the temples, but his eyebrows are still brown. His children—the ones who were napping in that hotel room when he jotted down his Darwinian inspiration—now have children of their own, and he has the "I ♥ Grandpa" coffee mug to prove it. A hospital lanyard around his neck, he rolls up his crisp shirtsleeves and settles down at his desk. Outside his office, roughly 30 scientists and PhD students spend their days researching patterns of cancer growth using equations like those describing population dynamics.

To Gatenby's knowledge, no one had endeavored to exploit evolution against cancer in a clinical trial until he developed his prostate cancer experiment. He picked prostate cancer to test this approach partly because, unlike other cancers, a routine blood draw for a molecule called prostate-specific antigen (PSA) can offer an immediate proxy for the cancer's progression.

To design a clinical trial, Gatenby and his Moffitt collaborators first needed to account for their idea that tumor cells vie against each other for resources. They turned to game theory to plot this dynamic and plugged the numbers into the Lotka-Volterra equations. The computer simulations they ran with these equations estimated how quickly drug-resistant cells would outcompete other tumor cells when exposed to the continuous dosage of Zytiga typically given to advanced-stage prostate cancer patients.

In the simulations, the typical administration of the drug led to drug-resistant cancer cells rapidly running rampant. The treatment would ultimately fail each time. That bleak outcome matched up with the results seen in hospital records. In contrast, the computer simulations suggested that if Zytiga were administered only when the tumor seemed to be growing, then the drug-resistant cells would take much longer to gain enough advantage to overrun the cancer.

In 2014 the Moffitt team managed to get the first small study to test this adaptive therapy approach off the ground, recruiting Robert Butler and a small group of other men with advanced prostate cancer. Butler's oncologist explained to him how it would work. He would remain on the Lupron he'd taken for years, and each month he would go to the hospital to get his PSA level tested, to judge whether his prostate tumor was growing. Every three months, he would get a CT scan and a full-body bone scan to watch for disease spread. Whenever his PSA level edged above where it stood when he entered the trial, he would start taking the more powerful Zytiga. But when his PSA level fell to under half of the baseline, he could go without Zytiga. This is appealing because Zytiga and drugs like it can cause side effects like hot flashes, muscle pain, and hypertension.

The Moffitt approach also promised to be far cheaper than taking Zytiga continuously. When purchased wholesale, a one-month supply costs almost $11,000. Butler had health insurance, but even so, his first month's supply each year would set him back $2,700 in out-of-pocket copayments, and $400 a month thereafter. Going off the drug whenever his PSA level was low would translate to huge cost savings.

Butler was participating in a so-called pilot trial, which was less rigorous than a large clinical trial, because it didn't randomly assign patients to receive the experimental or standard treatments. Rather, the study relied on a group of patients treated outside the trial as well as

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Robert Gatenby, a radiologist, saw patients suffer from intensive breast cancer treatments. He felt there must be a better way to treat cancer, to outsmart it rather than carpet-bomb it.

Mark Sommerfeld

results from a 2013 paper on Zytiga to come up with a benchmark for how patients typically fare when receiving continuous dosing of the drug.

When the early results of their new trial trickled in, the Moffitt scientists were gratified and relieved. Ahead of the trial, “we were, to be honest, terrified,” Gatenby says. The benefit of adaptive therapy appeared to be huge. Of the 11 men in the study, one left the trial after his disease spread, but most were living longer than expected without their cancer progressing. Men getting continuous dosing of Zytiga go a median of 16.5 months before the cancer becomes resistant to the drug and spreads. In comparison, the median time to progression for the men receiving adaptive therapy was at least 27 months. Moreover, they were on average using less than half of the standard amount of Zytiga. Joel Brown, an evolutionary ecologist and one of Gatenby's collaborators, said the team felt a moral obligation to get the word out: “The effect was so big that it would be unethical not to report it immediately,” he says.

They published a report in 2017, far earlier than anticipated, to a generally positive reaction from prostate experts—particularly because it suggested a way that people with cancer might live longer with less medication. “If you can reduce side effects, I think that’s fantastic,” says Peter Nelson, an oncologist who studies prostate cancer at the Fred Hutchinson Cancer Research Center in Seattle. “Conceptually it’s a beautifully simple approach.” Jason Somarelli, a biologist at the Duke Cancer Institute, calls Gatenby a pioneer: “He’s turning cancer into a chronic disease.”

Butler, who is 75, has gone for long periods off Zytiga—with stretches lasting as long as five months. “I’m now the poster boy, they say,” Butler says. He’s one of the best responders in the study.

Some doctors are already trying adaptive therapy on patients outside of clinical trials. In 2017 a doctor in Oregon, inspired by Gatenby’s pilot study, started a prostate cancer patient on a modified version of the approach when he refused the standard continuous dosing. She has since started treating a second man using adaptive therapy. Other oncologists might be doing the same. It’s nearly impossible to know for sure, because adaptive therapy doesn't require government approval. The protocol uses already-approved medications, and the US Food and Drug Administration doesn't police specific dosing schedules.

Experts urge caution, however. The prostate cancer study was very small, and without a randomly assigned control group the results aren't truly reliable. While the majority of the men in the trial remain stable, four more saw their cancer progress since the paper came out. "This is an approach that now needs to be carefully studied in prospective clinical trials before it is adopted into clinical practice," says Richard L. Schilsky, chief medical officer for the American Society of Clinical Oncology. Years could pass before a large-scale test of adaptive therapy takes place. Len Lichtenfeld, interim chief medical officer of the American Cancer Society, echoes Schilsky's concerns. "Is it intriguing? Yes," Lichtenfeld says. "But there is still a long way to go."

Gatenby agrees that adaptive therapy needs rigorous testing. He conveys a kind of humility you don't see very often in the upper reaches of medical science. He told me multiple times that he is not an interesting subject to write about, and more than once I heard close colleagues mangle the pronunciation of his name (which is pronounced GATE-en-bee); apparently he had never corrected them. But when he believes in something, he doesn't relent. And he believes in adaptive therapy. "He's like a teddy bear, but underneath that soft exterior he's made of steel," says Athena Aktipis, who studies theoretical and cancer biology at Arizona State University and has collaborated with Gatenby.

Late last year, Gatenby presented his work at a meeting of prostate cancer specialists. In the question and answer session afterward, an attendee shared his surprise at the results. "I guess what you're saying is that we've been doing it wrong all these years," the man mused, according to Gatenby. "I was literally speechless for a few moments," Gatenby admits, "and then I said, 'Well, yeah, I guess that's what I'm saying.'" He is still dwelling on the exchange and wishes he could somehow find the man and apologize. He's not taking back what he said; he does think the profession can do better. But, he says, "I should have been more diplomatic."

I

In 2016, a couple dozen researchers gathered in a conference room at an ultramodern genetic sequencing center along the banks of the River Cam, 9 miles outside of Cambridge, England. The gathering brought together experts to discuss how principles of ecology might apply to cancer. When they took a break, their idea of fun was to play a round of "Game of Clones," in which a small group of scientists pretended to be cancer cells trying to persuade the maximal number of other researchers bouncing around the room to be their malignant clones.

During this meeting, one overarching theme kept popping up: Evolution doesn't operate the same way within all cancers. It's not even clear that Darwinian natural selection always determines the genetic mutations that abound within a tumor. A study of colon cancer samples conducted by one of the conference attendees, Andrea Sottoriva of the Institute of Cancer Research in London, and Christina Curtis, a computational biologist at Stanford University, suggested a different pattern.

When colorectal tumors begin to form, there seems to be a "big bang" of mutations. This initial explosion of cellular diversity in these colon cancers seems to be followed by a period in which random genetic changes arise and become more prevalent out of pure happenstance rather than because the mutations confer some sort of competitive advantage. It's still unclear whether adaptive therapy, which operates on the assumption that there's Darwinian competition between tumor cells, would work well for cancers where the mutations arise continuously by chance.

Still, a kind of consensus emerged, and a year after the Cambridge meeting, the organizers published a statement outlining how cancers might be better classified. Twenty-two researchers—some of the biggest names in the field of evolutionary oncology, including Gatenby—coauthored the document.

One important factor in the group's suggested classification scheme is a measure of how swiftly a cancer is mutating. In the past decade, faster DNA sequencing tools have shown that Nowell—Gatenby's old professor, the cigarette-smoking pioneer in applying evolutionary thinking to cancer—was prescient: Individual tumors often bristle with rapid-fire genetic changes. Rather than two or three initial errors setting off a chain of uncontrolled growth, many tumors are the result of several series of mutations. A significant experiment published in 2012 found at least 128 different DNA mutations in various kidney tumor samples from one patient, for instance. There's some evidence that the more mutations there are, the more aggressive a cancer tends to be, suggesting a higher chance that one of these DNA changes will confer tumor cells with the potential to be drug-resistant. Given technological advances, it's not too far-fetched to think that within the coming decade, doctors will routinely measure the amount of mutations in their patients' tumors.

Today most cancers are assessed using a system that dates back to the 1940s. Doctors typically evaluate factors such as whether a cancer has spread to lymph nodes or beyond and on the basis of these attributes determine its "stage." On one end of the spectrum are stage 1 cancers, which are relatively confined, while at the other end are stage 4 cancers, which have spread extensively. Crucially, this system of assigning cancer a stage doesn't formally

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take a cancer's genetic mutations into account.

The suggested categorization system that grew out of the Cambridge meeting would look at cancer in a completely new way. Rather than four stages of cancer, the authors of the 2017 consensus statement propose no less than 16 different categories—for example, tumors that have slow cell turnover and a low rate of accumulating mutations, or tumors that are a hotbed of genetic diversity with quickly replicating cells competing for resources. This latter type of tumor might be the most likely to evolve a way to outcompete drug-sensitive cells in the body and thereby could, in some cases, be the most dangerous. A fast-moving cancer of this kind might also be the best candidate for adaptive therapy.

Around the time the consensus statement came out, Gatenby and his collaborators in Tampa were hard at work running cell experiments in a lab down the hall from his office. The goal was to prove a key tenet of adaptive therapy. Gatenby's approach assumes that when treatment is removed, drug-resistant cancer cells will replicate more slowly than drug-sensitive cells. The theory rests on the assumption that those resistant cells need lots of energy to maintain their armor against the medication meant to kill them. During treatment breaks, the thinking goes, the fuel-hungry resistant cells are outcompeted by drug-sensitive cells, which need fewer resources to thrive.

To gather evidence for this idea, Gatenby's research team placed human breast cancer cells with resistance to the drug doxorubicin in a petri dish alongside an equal-size population of doxorubicin-sensitive breast cancer cells and watched the two groups fight for resources. By day 10 the resistant cells made up only 20 percent of the cells in the dish and continued to slowly decline from there. At the end of the experiment, published last year, these resistant cells had dropped to around 10 percent of the total population.

Granted, this experiment happened in a petri dish, not a human body—or even the body of a lab rat. Some leading cancer specialists agree with Gatenby that drug-resistant cells are likely outcompeted by other cells when cancer medication is withdrawn. But, say others, what if Gatenby is wrong? What if resistant cells actually thrive during the period when the patient is taken off drugs? The risks are high. No one wants to hasten death.

R

`Rethinking cancer as a chronic illness requires a` mental shift—a shift that other changes in cancer therapy might be easing. There's a practice of letting cancer patients take doctor-supervised "drug holidays" from their medications, for instance. And we've adapted our thinking when it comes to medicine before. Doctors once thought that stress was the primary culprit behind ulcers, but biologists uncovered a bacterium as the main cause. More recently we've gotten used to the weird idea that trillions of bacteria live in our gut microbiome.

Perhaps, then, it isn't a huge stretch to think we might tolerate coexisting with cancer cells as long as we can prevent them from growing unchecked. Whereas Darwin put forth ideas about what has become known as macroevolution—the rise and fall of species, whether they be beetles or bald eagles—this new view of cancer could be an example of what we might call "endo-evolution": natural selection playing out within an organism's own tissues.

The American Cancer Society acknowledges that some cancers are already managed as chronic illnesses. In certain cases, doctors simply try to keep the malignancies from spreading with new rounds of medication. Gatenby's adaptive therapy aims to take the guesswork out of the treatment. More trials at Moffitt are in the planning stages or underway for cancers affecting the breast, skin and thyroid, in addition to a new, bigger trial in prostate cancer patients. Across the country, in Arizona, Athena Aktipis and her husband and scientific collaborator, Carlo Maley, have secured a grant to begin a breast cancer trial using adaptive therapy in conjunction with a local branch of the Mayo Clinic.

But the idea of cancer as an implacable enemy that needs to be annihilated runs deep. Even Gatenby feels it, particularly when it comes to children. When his daughter was a teenager, one of her classmates died from a form of cancer called rhabdomyosarcoma. He never met his daughter's friend but heard about his decline. Then, last year, a pediatric oncologist at Moffitt approached him to see if therapy inspired by evolutionary theory might work to fully weed out cancer from children newly diagnosed with that same disease. In the highest-risk group, that cancer kills as many as 80 percent of patients within five years.

In October, they met to begin designing a study. This trial will use a more sophisticated evolutionary model to cycle patients on and off of several drugs. The hope is to deploy the additional drugs to kick the cancer while it's down, and thereby drive it to extinction. It's an ambitious goal.

For now, Gatenby is most focused on managing advanced cancers in adults, and doing so as a chronic disease. In that sense, he's challenging the words emblazoned on the outside wall of the Moffitt Cancer Center: "To contribute to the prevention and cure of cancer." Robert Butler has pondered these words too, which he passes when walking into the building for checkups and treatments. "Certainly, in my case there's no intention of cure. What we're doing is control. So that's not really the correct logo anymore, is it?" he says. Butler tells me about a time when he and some of the Moffitt researchers brainstormed alternative slogans. "We finally came up with 'Our aim is to make you die of something else'—which I thought was lovely," he adds. "It's more true."

STRANDS OF EVIDENCE

Two decades ago, a new form of genetic testing helped send a man to prison. His case shows what happens when juries grapple with perplexing science.

By Jessica Wapner

Art by Emon Toufanian

Barbara Schmidt keeps a box of newspaper clippings under her bed. It's a cheap plastic container with a light-blue lid. She rarely opens it. The photocopies inside, some of them labeled in her tidy script, are cut into rectangles of various sizes, neatly trimmed to frame the only story on the page that she cared about—that of her husband's arrest, trial, and conviction for attempted murder in Lafayette, Louisiana, more than two decades ago. She isn't sure why she clipped the articles in the first place, or why she still stores them within arm's reach. "I just felt compelled to do it," she says. One thing she's always been sure about, though, is her husband's innocence. She is like a mama bird: petite, protective of her family, loyal to her mate. "I chose to stay," she says.

Just off Barbara's kitchen is the room that her husband, a gastroenterologist named Richard Schmidt, used as his study before he went to prison. For her, this is where the story begins. On a hot July day in 1995, she came home to find several plainclothes police officers rummaging through Richard's papers. She asked what they were looking for. "Evidence of B12," she remembers them saying, with no further explanation. She called her husband at work to find out what was going on. The investigators had showed up there too. "He seemed clueless," she recalls.

It didn't take long for all the sordid details to emerge. The police were investigating a complaint by Janice Trahan, a nurse who had worked at Schmidt's practice and had a decade-long affair with the doctor. As Trahan later testified in court, Schmidt had entered her house on the night of August 4, 1994, soon after she'd ended their relationship. She and her 3-year-old son were asleep in bed. Schmidt had woken her up, saying he wanted to give her a vitamin B12 shot, something he'd occasionally done during their relationship when she wasn't feeling well. Trahan protested. Schmidt insisted. He pushed the needle into the muscle of her upper arm, depressed the plunger, and quickly left the house. Several months later, Trahan started feeling ill and was eventually diagnosed with HIV. She believed that Schmidt, in a fit of jealousy, had injected her with tainted blood from one of his patients.

Barbara has a different recollection of August 4, 1994, one she described to both the police and later the jury at her husband's trial. The family had recently returned from a trip to Florida, she says, and Richard had injured his back lifting heavy luggage off the carousel. A record in her checkbook reminded her that she'd gone out to buy new knobs for the kitchen cabinets that day, which she had to show him as he lay in bed. "He wasn't crazy about them," she says. After that, Barbara maintains, she showered and they both went to sleep. (The Louisiana Department of Corrections declined to make Richard Schmidt available for an in-person interview.)

When the police searched Schmidt's office, however, they found something strange. Buried beneath a mound of old files was the notebook in which his nurses had recorded the previous summer's blood draws and other lab work. Curiously, the notebook was only half full. The final entry showed that an HIV-positive patient had come in for an appointment on August 4. He had been scheduled for a blood draw, but the notebook didn't confirm whether it actually took place. The police theorized that Schmidt had taken his patient's blood, with or without the help of a conspiratorial nurse, and kept the vial hidden so he could use it on his former lover. Still, the evidence was circumstantial. One of Schmidt's nurses, in her testimony, described the notebook as "just a jot sheet," not an official record. The prosecuting attorney, Keith Stutes, needed harder proof.

At the time, the US justice system was in the midst of a forensics revolution. Just over a decade earlier, in 1983, scientists had invented a technique known as polymerase chain reaction, or PCR, which made it possible to copy DNA from tiny samples of blood or tissue in large enough quantities to study. Within a few years, investigators in England had used DNA profiling to prove that a teenager who'd confessed to two rape-murders had not committed the crimes; they also used it to identify the man who did. The first US case came a year later. Soon enough, DNA testing was everywhere you looked, according to attorney Barry Scheck, who in 1992 cofounded the Innocence Project, which exonerates wrongfully convicted people using DNA. One judge called it "the single greatest advance in the search for truth since the advent of cross-examination."

For Stutes, then, it made sense to turn to genetics. "We were conscious that DNA could make comparisons of body fluids," he says. "The question was, is there a science that will be able to compare the viruses?" The criminologists his office usually worked with didn't have an answer, but they recommended that he contact Michael Metzker, a graduate student at Baylor College of Medicine, who was developing technology for studying the transmission of HIV as part of his thesis work. As Metzker recalls the conversation, Stutes asked him "whether two strains from different individuals could be matched" using some sort of test. Not that he knew of, Metzker told Stutes. But there was a technique that could parse the relationship between two different viruses. It was called phylogenetics.

* * *

Just as each living person occupies a branch on a family tree extending generations back in time, so does each living organism. These trees, called phylogenies, tell us that humans once shared an ancestor with mushrooms, giraffes with beetles, elephants with elephant shrews. Modern phylogenetics got its start soon after Darwin published *On the Origin of Species*, but its potential wasn't fulfilled until the 1990s, when biologists gained the ability to sequence DNA cheaply and run the long strands of genetic code through complex computer algorithms. With these tools, they could re-create the evolutionary history of any organism on earth. And they weren't limited to the broad strokes of change that occur over eons or millennia. They could also track the person-to-person movements of modern pathogens, tracing an outbreak of swine flu to the town where it originated, uncovering the trade routes that brought hepatitis C to the United States, and probing new hot spots of HIV infection.

Indeed, HIV is a good fit for the technique. Its genetic material is made from RNA, which mutates much faster than DNA, producing new strains at a furious pace. Each of the 30 million or so persons currently living with HIV harbors a slightly different variant. Even the tiny virus particles circulating in an individual's bloodstream differ, if ever so slightly, one to the next. But within a given geographic area, each risk group—intravenous drug users, men who have sex with men—tends to carry a similar strain. In the early 1990s, a few years before Stutes approached Metzker, a phylogenetic analysis led by the Centers for Disease Control and Prevention suggested that a dentist in Florida had infected six of his patients with HIV. They constituted their own miniature risk group—in phylogenetic terms, their own small branch of the giant tree.

Metzker planned to mimic the CDC's approach in the Florida case. If he found that Trahan's virus closely resembled that of the HIV-positive patient in Schmidt's notebook, her accusation would be supported. If, on the other hand, the connection was distant, then her account would seem weaker. The police sent Metzker blood samples from Trahan, Schmidt's patient, and about 30 other HIV-positive people from the local area; this last group would serve as a scientific control, allowing Metzker to gauge the relative similarity of all the strains.

HIV hides out in its host's own genome, switching from RNA to DNA after it successfully infects a cell. Metzker isolated some of these cells from each sample, extracted their DNA, and used PCR to create huge quantities of copies. Then he sequenced the DNA and created a tree. The first two strains, Metzker concluded, were more similar to each other than to any of those in the control group. Some of the sequences were identical, with portions of the patient's HIV DNA showing up in Trahan—a phenomenon called nesting. It was as though her virus had lifted a verse from his genetic song.

The results gave Stutes the evidence he'd been looking for. On July 23, 1996, a year after the police searched Schmidt's home, the doctor was arrested on charges of attempted murder. The case immediately became what one local headline referred to as a "media magnet." Schmidt's eldest daughter was in the family's backyard pool when she heard the news; her brother's girlfriend called to say she'd seen their father on TV. (Now a 39-year-old lawyer in Lafayette, the daughter still hesitates to tell people her maiden name.) Producers from *20/20*, *Dateline*, and *The Montel Williams Show* jockeyed for interviews. "The newspaper articles all tainted Richard in a negative way," says Schmidt's Bronx-born defense attorney, Mike Fawer. And Schmidt, with his helmet-like black toupee, thick brows, and heavy-lidded eyes, fit the part. "They made him look so sinister," Barbara says.

Schmidt's case marked the first time that a US criminal court would consider phylogenetic evidence. At his pretrial hearing, which began on December 6, the defense and the prosecution argued over whether Metzker's analysis was admissible—in part, whether it met the guidelines established by the US Supreme Court in a 1993 case called *Daubert v. Merrell Dow Pharmaceuticals*. In *Daubert*, the court advised that a forensic test should be presented to a jury only if the methods on which it was based had been published in a peer-reviewed journal and gained "widespread acceptance within a relevant scientific community." In addition, the court said, the test should have a known error rate.

After several days of testimony, the judge, Durwood Conque, ruled that Metzker's analysis met the *Daubert* criteria. He stipulated, however, that the phylogenetic evidence could be used only to show that two HIV sequences were related. It could never establish the "likelihood or suggestion of direct transmission," he said.

To the defense team, even this qualified acceptance seemed improper. "I thought we were going to win on the *Daubert* hearing," Fawer says. "But we got the back of the hand." Phylogenetics was far from a proven forensics tool. Its only prior use in a criminal court had been to investigate a rape conviction in Sweden. And while a description of the Florida dentist study had been published in *Science*, a peer-reviewed journal, in 1992, that case involved civil charges, not criminal ones, and never went to trial. That left little basis for the scientific community to accept the method or discern its susceptibility to error. In fact, Metzker believes that one of the reasons Stutes hired him, an inexperienced graduate student,

Schmidt, with his helmet-like black toupee and heavy-lidded eyes, fit the part of the villain.

Previous spread: John Rowland/Lafayette Daily Advertiser via USA TODAY NETWORK (Schmidt); Lafayette Daily Advertiser File via USA TODAY NETWORK (newspaper); Getty Images (red texture)

was that more seasoned scientists did not want to be involved with what they considered a controversial practice.

Schmidt's trial began in mid-October 1998. It was held in the courthouse in downtown Lafayette, a huge block of concrete rising from a manicured lawn. The 12 jurors heard Janice Trahan, now known as Janice Allen, describe her tumultuous relationship with Schmidt—his "obsessed, jealous, controlling, volatile" behavior, the "extremely painful" shot he'd forced upon her. They heard Jim Craft, the lead detective investigating Trahan's accusation, discuss the memory recall techniques he'd given her to help her remember the date of the alleged injection. They heard Barbara Schmidt's conflicting account of that date. The doctor himself never took the stand, never discussed the odd notebook. "It surely was not clearly explained," Fawer, the defense attorney, acknowledges.

Finally, it was time to present the forensic evidence. Five expert witnesses eventually took the stand. The transcripts of their testimonies read like a molecular biology textbook: There are complex discussions of statistical significance, "bootstrap values," "branch lengths," and "gene loci." Even the more accessible arguments are delivered in all but impenetrable language. A defense witness named Bette Korber, one of the country's top phylogeneticists, gave a lengthy and complicated testimony that included cases from Thailand, Amsterdam, and a large US database. Eventually she offered her succinct take on the HIV sequences from Trahan and Schmidt's patient: "I would say that they are probably unrelated." But, in the transcript, this insight comes toward the end of 50-plus pages of technical science.

One academic stood out from the rest. David Hillis, an evolutionary biologist at the University of Texas at Austin, had advised the CDC on phylogenetics and edited *Systematic Biology*, one of the field's most prestigious journals. "I was very impressed with him," says Stutes, who calls him "a powerful witness." At the prosecution's request, Hillis had performed his own analysis of the HIV samples, attempting to replicate Metzker's findings. When he took the stand, Stutes asked him what he had discovered.

Hillis spoke plainly. The HIV sequences in Trahan and Schmidt's patient were, he told the jury, as closely related as two sequences isolated from different individuals could be. He was unflappable in the face of Fawer's grilling. Toward the end of the cross-examination, Hillis testified that "there's less than a one in a million chance you'd see the association that you did at random." The prosecutor liked this line so much that he used it in his closing arguments. Twenty years later, Barbara is still haunted by it. She believes that those words—"one in a million"—more than any others, stayed with the jury, possibly because it was the only phrase they could easily understand. Trahan remembers it too.

On October 23, 1998, the jury found Schmidt guilty of attempted second-degree murder. (Ten of the 12 jurors agreed; until last November, a Jim Crow–era law in Louisiana allowed for convictions that were not unanimous.) Four months later, he was sentenced to 50 years in prison.

* * *

The process of moving science from the cloistered realm of the laboratory to the messy environment of the courtroom is inevitably fraught. Although criminal law readily embraced DNA forensics at first, debate arose quickly. In 1989, Barry Scheck questioned the legitimacy of a test linking blood from a murder victim to blood on his client's watch. That first challenge marked the start of a battle. "People talked about it being the DNA Wars," says Simon Ford, a research scientist at Forensic Bioinformatics, a firm that seeks to "cast light into the black box of forensic analyses." By 1992, the same year the Innocence Project began, the tension had spurred the National Research Council to draw up formalized guidelines. Among other things, those guidelines advised experts to stop saying that DNA testing was infallible.

Forensic phylogenetics never got its own NRC report. In part that may be because, unlike DNA profiling, it is rarely invoked in court. The technique is used only in cases of criminalized HIV or hepatitis C transmission, and not all attorneys seek it. There are no designated crime labs, no special training protocols for witnesses. The only existing recommendations are in piecemeal publications by small groups of academics. Amid this sparse landscape, Schmidt's case stands out. Anne-Mieke Vandamme, a Belgian biochemist and leading expert in forensic phylogenetics, calls it a "textbook case"—proof that the technique works. But she and others also see it as a warning sign, an example of what can happen when complex, unfamiliar science is brought before juries.

At the time of Schmidt's trial, defense witnesses raised several possible issues with Metzker's study. For one thing, his lab notes referred to Trahan and Schmidt's HIV-positive patient by their first names, which meant he knew which sequence belonged to whom, potentially skewing the results. What's more, the defense witnesses argued, Metzker didn't take the proper precautions with his PCR analysis. DNA fragments have a way of flying around the laboratory once the PCR test tubes are opened. They "can fall on pipettes, gloves, bench tops, into other tubes," says microbiologist James Mullins, who worked on the Florida dentist case and testified at Schmidt's pretrial hearing. Once that happens, tracking the fragments back to their sources becomes about as easy as figuring out which log the ashes in your firepit came from. DNA from different sequences can easily become mixed. That's why "you shouldn't ever work on both subjects in the same laboratory," Mullins adds. Metzker didn't follow this protocol either.

Today, he acknowledges both oversights. "We should have blinded it," Metzker says, using the technical term for when scientists mask information about their test subjects to avoid bias. Yet he notes that Hillis' follow-up study, which *was* blinded and used newly drawn blood samples, came to the same conclusions. Hillis observed the right PCR protocols too. "The truth of the matter is we've done our due diligence," says biologist David Mindell, who assisted Hillis with the work.

But not all the questions hovering around the results were addressed by the second study. The defense also voiced doubts about a process called contact tracing, which seeks to uncover all possible transmission routes for an infectious disease. Trahan had volunteered the names of several men she'd slept with, all of whom the police confirmed did not have HIV. But that inquiry, the defense argued, wasn't equivalent to a rigorous probe by an expert epidemiologist. Trahan's work as a nurse in an intensive care unit, for instance, could have exposed her to the virus. Although Vandamme cautions that she isn't familiar with all the specifics of Schmidt's case, she says she'd likely have zeroed in on this weakness if she'd been asked to testify.

At the pretrial hearing, Mullins also contended that there were problems with the control group, the HIV-positive patients from around Lafayette. The ideal forensic phylogenetic study, he says, draws its controls from the same risk group as the accuser—in this case, Trahan—and from people infected around the same time. But in Schmidt's trial, nearly two-thirds of the samples came from gay men, some of whom had tested positive up to 10 years earlier. Had they come from a wider pool, Mullins says, Metzker might have found strains even more closely related to Trahan's HIV than the one circulating in Schmidt's patient, who was a gay man. That wouldn't necessarily have absolved Schmidt, but it might have broadened the jury's perspective.

> **You can believe in Schmidt's guilt and still see problems with how the evidence in his case was handled.**

Hillis balks at this. For him, the fact that Trahan's sequences were embedded, or nested, within the patient's sequences is indisputable evidence of their relatedness. "This could only have happened if the physician's patient was the source of the infection in the sample from the victim," he says. An expanded control group, he adds, would not have made a difference.

John Huelsenbeck, a phylogeneticist at UC Berkeley, is unwavering in his belief that the jury in Schmidt's case "made the right decision." Like Hillis, he sees the nesting as decisive. "That's all that matters," he wrote in an email. Vandamme holds a similar view. In general, she says, phylogenetics can only uncover whether there is a close relationship between two strains, not which one came first—just as Judge Conque advised the jury during the pretrial hearing. But the nesting phenomenon transcends this restriction, allowing for the conclusion that Schmidt's patient's virus was older than Trahan's.

Yet even that seemingly pivotal piece of evidence goes only so far. Vandamme emphasizes that the nesting doesn't eliminate the possibility of an intermediary between Schmidt's patient and Trahan. "You can never prove that one infected the other," she says. In the early days of forensic phylogenetics, she adds, the few juries that encountered it sometimes got the mistaken impression that an analysis showing a connection was proof of guilt. But the science can't ever show that. "You can do the best possible phylogenetic analysis," she says. "It's still not going to prove transmission."

It's not uncommon for questions to linger after a criminal conviction, particularly when the charges are as serious as attempted murder. You can believe in Schmidt's guilt and still see problems with how the scientific evidence in his case was handled. But beyond the complex debates about PCR methodology, contact tracing, and all the rest, Vandamme says her biggest concern about forensic phylogenetics may be that academics don't always "have sufficient appreciation for how what they say is interpreted by the jury." Mullins, the defense witness, maintains that Hillis crossed a boundary with his "one in a million" comment, using persuasive language that may have caused the jury to lend phylogenetics more weight than Judge Conque intended—or than the science warranted. "He really stretched credulity," Mullins says. "It was an overreach." One juror, who asked to remain anonymous, says, "I think the DNA was probably the major reason, and the other evidence just supported that."

Schmidt appealed his case multiple times, mostly on the basis of allegedly flawed phylogenetic evidence. In 2000 the Louisiana Court of Appeals denied his request, finding that the circumstantial evidence was enough to eliminate reasonable doubt even without the science. Two years later, the US Supreme Court declined to hear his case, offering no comment for its decision. The Louisiana Supreme Court denied another appeal in 2005. Schmidt and his attorneys continue to fight the verdict, though they know they are unlikely to succeed. He will be eligible for early release in 2023.

Among the clippings in the box under Barbara Schmidt's bed is a single photograph of her and her husband. They look like they're headed for a night out, he in a shirt and tie with his arm around his equally well-dressed wife. But in fact they're leaving the courthouse after a day of pretrial testimony—the fateful first chapter in a textbook case.

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AN INVESTIGATOR SET OUT TO DISCOVER THE SOURCE OF ONE SCAMMY ROBOCALL. TURNS OUT, HIS TARGET MADE THEM BY THE MILLIONS.

BY
ALEX W. PALMER

MOLLY MENDOZA

PRESS 1 TO HEAR MORE

PART ONE

BRAD YOUNG, A LAWYER AT TRIPADVISOR, ARRIVED AT THE company's offices in Needham, Massachusetts, on October 12, 2015, to find an email from his boss, Seth Kalvert, the company's general counsel. In itself that wasn't strange. As a travel site built on crowdsourced wisdom, where hundreds of millions of ordinary people post reviews and rate businesses, TripAdvisor is susceptible to fakery meant to inflate the ranking of a so-so restaurant or stain the reputation of a storied hotel. Young oversaw a group responsible for fending off these efforts, so he frequently got questions from Kalvert about con artists, cunning new deceits, and other shady corners of the law.

But this email was different. Kalvert's wife had received a robocall offering an exclusive vacation deal as a reward for her loyal accumulation of "TripAdvisor credits." That would have been nice if TripAdvisor credits were a thing, but they weren't. The call was also odd because TripAdvisor didn't engage in telemarketing, much less robocalling. Kalvert wanted Young to look into it.

The anti-fraud team was, in Young's words, "the company's secret sauce," adept at tackling every deception the internet had to offer. But the hustle meant to entice Kalvert's wife relied on old-school telephony. Cracking it would require an unusual set of skills. Luckily, Young knew just the person to turn to.

Fred Garvin had joined TripAdvisor's anti-fraud team eight years earlier. He'd been employed in a series of short-term jobs: mechanic, audio editor, anything that seemed interesting enough to hold his attention for a while. He was out of work when a friend saw an opening for a content moderator at TripAdvisor and urged Garvin to apply. He worked at home for a while, under the radar, but pretty soon managers started noticing his obsessive streak and a knack for what he called "research." As a kid growing up in a small New England town in the pre-internet era, he'd tracked down the addresses of celebrities so that he could request an autograph; he got a postcard signed by the B-52s and one from Mr. Bill, a famous *Saturday Night Live* character from the 1970s. (The name "Fred Garvin" is another *SNL* reference, one of several professional aliases he adopted to protect his identity from the scammers and fraudsters he chases. It comes from an old sketch with Dan Aykroyd as Fred Garvin, male prostitute.) Garvin's manager recommended him for a position with the anti-fraud team. "He's the most cynical person I've ever met," she said. "He will question everything." He was a perfect fit.

Young asked Garvin to look into the suspicious phone call. He said he figured it was probably the work of "some two-bit hustler" and wouldn't take long to sort out. Garvin, though, had only one phone call to go on, and a simple question: Who was on the other end of the line?

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PART TWO

BEFORE YOUNG TASKED HIM with running down the robocaller, Garvin had not taken much interest in the practice. Robocalls have been around since at least the 1980s, when someone first thought to attach a tape deck to a phone. In the analog age, the hardware was clunky, expensive, and difficult to operate. The tapes had to be rewound, and they eventually wore out. Still, the technology improved, and telemarketers kept promoting their wares. By the early 1990s, Americans were so sick of telemarketers and prerecorded messages that when US senator Fritz Hollings lamented on the Senate floor that the calls were "the scourge of modern civilization," few challenged the assertion, despite the competing scourges of war, say, or the spread of AIDS.

Hollings was the sponsor of the Telephone Consumer Protection Act, and he seemed to draw upon personal experience during the legislative debate on the bill: Automated calls "wake us up in the morning, they interrupt our dinner at night, they force the sick and elderly out of bed, they hound us until we want to rip the telephone right out of the wall." The law was signed by George H. W. Bush in 1991 and limited how and when telemarketers could place calls, focusing mostly on landlines, the dominant technology of the time. Cell phones, still relatively new, were treated like emergency lines and bestowed with special protection.

Then over the next two decades came the internet, cheap data, voice-over-internet protocol, and the deregulation of the telecommunications industry—all a boon to consumers and robocallers alike. Even big, well-known companies got in on it, launching robocall campaigns as a form of mass marketing on the cheap.

Not surprisingly, people complained about being inundated with calls, and in 2009 the Federal Trade Commission enacted the "robocall rule," which banned most prerecorded telemarketing calls. There were exceptions, though, for things like political campaigns, charities, and debt collection, meaning your bank can still pester you about unpaid bills and candidates can beg for your vote.

But the law was quickly outpaced and overshadowed by the rapid evolution in technology. Today, a single person in a modestly equipped office can make millions of calls a day by renting some server space, installing off-the-shelf autodialing software, and paying a VoIP provider to transmit calls. Some of the software is open source, and VoIP carriers often advertise a month of free service as a way to entice potential customers. Software companies offer everything you need in one package—a robocall starter kit, available for anyone to buy.

Best of all, it's cheap: VoIP services cost three-fifths of a penny per minute, and that's only if the call is answered. Unscrupulous carriers openly advertise their services to those looking to make "dialer/short duration termination calls"—the jargony euphemism for robocalls—and databases of consumer phone numbers are easy to buy. "The technology has gotten so inexpensive that any person can become a robocaller overnight," says Ian Barlow, who coordinates the FTC's Do Not Call program. "It's easy, it's accessible, and there are no barriers to entry." Once the software has been programmed to control who to call and when, the robocaller doesn't even need to press a button to start making calls each morning. The same technology also makes scammers hard to identify and track down.

Little wonder, then, that the United States is awash in robocalls. According to YouMail, a maker of robocall-blocking software, Americans received a record-breaking 47.8 billion robocalls in 2018. That works out to nearly 200 per year for every adult. Unwanted calls are the most common consumer complaint lodged with the Federal Communications Commission, and the trend shows no signs of slowing, despite the pile-on of laws and regulations—the Telemarketing Sales Rule, the Truth in Caller ID Act, and the Telephone Consumer Protection Act, among others—outlawing the vast majority of autodialed calls or prerecorded messages, at least those used for marketing purposes. With more than 100 million calls placed every day, robocalling might well be the most ubiquitous, most hated, and least punished crime in the country.

GARVIN SET UP SHOP IN A QUIET CORNER ON THE THIRD FLOOR OF TripAdvisor's headquarters, flanked by whiteboards and a bay of screens, preparing to track down the mystery robocaller. Garvin is in his early forties, with dark, spiky hair, a soft face, and darting eyes. In conversation, he is calm and self-possessed, even formal, but he buzzes with a tightly wound energy.

Garvin scoured the web, looking through blogs, forums, and social media for any mention of a similar call. He didn't have to look very far. Dozens of people were grumbling—or worse—on TripAdvisor's own forums. "IF I EVER GET A CALL LIKE THAT AGAIN, I WILL CONTACT THE FCC AND I WILL OPEN THE GATES OF HELL ON TRIP ADVISORS," one person wrote. "NEVER NEVER NEVER NEVER CALL ME LIKE THAT AGAIN. EVER. GOT IT."

One of his early gambits was simply calling a number that had placed a robocall. When he tried that, though, he found a human on the other end of the line, perplexed as to how their phone number had been used for prerecorded marketing. Eventually he figured out that the robocaller was engaging in a practice called neighbor spoofing—making the calls look as if they were coming from someone living near the intended recipient. For Garvin, it was a dead end.

Hoping he might get lucky and receive one of the robocalls himself, Garvin began answering every suspicious call and spoofed number that lit up his cell phone. He heard dubious alerts about student loan forgiveness, unclaimed lottery windfalls, and tax debt. "I was the only person you will ever meet who was excited to receive a robocall," he says. He was getting several a day and answering as many as he could, all the while hoping for one that would lead back to the TripAdvisor scam.

The irate stories on TripAdvisor forums seemed like promising leads, except that the details didn't line up. People who got the same prerecorded pitch on the same day were transferred to live operators who offered different vacation packages at different prices. Garvin and Young felt as if they were "chasing ghosts," Young said.

Those posts did offer a few clues: The calls came over VoIP and seemed to be a classic bait and switch. If you were on the line, you'd hear a recorded female voice saying that you'd received TripAdvisor credits that could be redeemed for a vacation. The "credits" might be for $999 or $2,000—the amounts differed—but you'd be instructed to press 1 to take advantage of the *incredible offer* and then be transferred to a live operator. Neither the credits nor the name TripAdvisor would be mentioned again. Instead, the operator would pitch an unrelated offer: a cruise, a resort, an all-inclusive stay at a beachfront hotel.

Drawing from angry postings and tips on the TripAdvisor forums, Garvin put together a list of all the companies pitching their wares through the fraudulent robocall. He checked the domain registrations and IP addresses of their websites and realized that they all had identical content, shared web hosting servers, and listed the same contact information. They all showed the same white sand beaches and featured images of the same beautiful, sun-dappled tourists. And they all traced back to the Yucatán. Cutting and pasting in Google Translate, Garvin trawled through Mexican business registration documents, time-share websites, and social media postings, mapping out an ecosystem of companies—some legitimate, some less so—that he had never known existed. Now, he thought, he was getting somewhere.

His internet wanderings led to a booming call-center industry in Cancún and surrounding areas connecting American customers with local time-share and resort companies. If these centers were involved in the robocall trade, Garvin wanted to learn as much about them as he could.

Facebook proved a useful investigative tool. One employee posted a photograph of himself posing in the call center. On the wall behind him was a piece of paper listing some sort of information. Garvin zoomed in and could just make out the business name and website address that the center's operators were to use that day—a lead for observing the scammers in real time. Over the following months, Garvin watched on Facebook as the man in the photo transitioned from employee to manager to entrepreneur, posting ads soliciting staff for his own newly opened call center. Garvin was down the rabbit hole now, snooping from afar on individual employees as they went about their business. He wasn't sure if these call centers were the ones responsible for the TripAdvisor scam, but the only way to find out was to keep tracking them.

Garvin picked up another clue: TripAdvisor was not the only brand being flogged. The calls also touted exclusive deals for loyal customers of Marriott, Hilton, and Expedia—a "who's-who of travel companies," Young says, none of which were actually offering the deals. In his conversations with jilted customers, Garvin found that the trips on offer were probably real but difficult to redeem. When someone tried to book a trip they had purchased, suddenly there were no dates available, or the contact information the business had provided was invalid. The customers who made it through that gauntlet were welcomed to their vacation destinations with long sales pitches for expensive local time-shares. The brand names had drawn people in. "They couldn't just say, 'Hey, you interested in a very questionable Mexican time-share situation?' " Garvin says.

Garvin managed to recruit some of the irate customers into his army of amateur sleuths. One woman, a nurse from Massachusetts named Kim, was getting 10 or more calls a day for months on end. "I was, oh, I was beyond, beyond irritated," she says. Finally, fed up, she found the phone number for TripAdvisor's president and CEO and called to complain. He called right back. "This is not us," he explained. "This is somebody pretending to be us." Then he put her in touch with Garvin, so he could debrief her and add the phone numbers she'd collected to his own burgeoning database.

The investigation was moving along. Young and Garvin were starting to see where the calls ended up and how people were getting scammed. But they still didn't know who was making the robocalls—or how to stop them. After more than three months of digging, they decided to ask for help.

HANGUPS:
LAWS OF ROBOCALLING

If your phone is ringing, there's a near 50 percent chance it's a robocall on the other end—and a 100 percent chance that you will be irritated if it is. Some 130 million robocalls are dialed each day. The first federal law against autodialed calls was enacted in 1991; limits and exceptions were patched in over time. Yet only a small fraction of robocallers are penalized. Why? Several reasons. Robocallers constantly change numbers, evading investigators. Enforcement is iffy. (As of April 2018, the Federal Trade Commission had fined telemarketers $1.5 billion for Do Not Call and robocalling violations combined, but collected only $122 million, or 8 percent.) The bottom line: Despite close to 4 million complaints a year, robocalls are on the rise. Here is a primer on some of the key prohibitions. —ZAK JASON

TELEPHONE CONSUMER PROTECTION ACT OF 1991

The original antispam law bans automatic dialing and prerecorded messages to cell phones, emergency lines, pagers, and guest rooms at hospitals, nursing homes, and health care facilities.

TELEMARKETING SALES RULE

In 2003 the government set up a Do Not Call Registry (donotcall.gov) to prevent unwanted phone marketing. (Some 235 million numbers are now on the list.) But there are exceptions for telephone surveys, debt collectors, airlines with "your flight was canceled" messages, and political and charitable organizations—which is why you can expect to get a lot of robocalls as the 2020 presidential election heats up.

TRUTH IN CALLER ID ACT OF 2009

In the early 2000s, robocallers learned how to make calls appear to come from neighbors or nearby area codes. This law bans that practice, though we don't have to tell you that it still happens all the time. In 2018 alone, the FCC issued more than $200 million in spoofing-related fines, including the $120 million against Adrian Abramovich. The agency has yet to collect a dollar.

PART THREE

IN APRIL OF 2016, YOUNG FLEW to Washington, DC, to meet with Kristi Thompson, deputy chief of the Enforcement Bureau at the FCC's Telecommunications Consumers Division. Young had pulled together the information that he and Garvin had been gathering, hoping to persuade the FCC to get involved in the hunt. He was surprised when, almost as soon as he began speaking, he says, "there was visible excitement throughout the room."

The FCC was chasing the same scammers. A few months earlier a medical paging company called Spok had come to the agency for help; a sudden influx of robocalls was flooding the company's network. Pagers may seem like an anachronism, but they are still used by more than 80 percent of hospitals. Whoever was behind the TripAdvisor robocall campaign had inadvertently debilitated Spok's networks by flooding pagers with digital messages they weren't equipped to handle. Emergency room doctors, nurses, and first responders were getting delayed alerts. This was not just an annoyance; it was a matter of life and death.

Thompson's team already had an idea where the calls were coming from. TripAdvisor "gave us the content of the messages, and the 'why,' " an FCC official who worked on the case says. "We knew the 'what,' but we couldn't see inside the messages like they could."

Young returned to TripAdvisor headquarters feeling buoyed. Garvin soon came to him with another reason to celebrate. On July 29 he had driven to his sister-in-law's house and was chatting in the front yard about dinner plans when his phone rang. Garvin saw a spoofed number and had an intuition. His sister-in-law was midsentence when Garvin blurted, "I have to go." He sprinted to his car, grabbed a notebook, and picked up the call.

"This is TripAdvisor," a chipper automated female voice said, and today was Garvin's lucky day: He'd been awarded thousands of TripAdvisor credits for an exclusive vacation to the sunny Caribbean!

It *was* Garvin's lucky day. He'd been collecting information for more than nine months, but everything he knew was secondhand. He had never heard the messages himself or been able to tie the Mexican resorts directly to the call centers and the fraudulent use of TripAdvisor's name. Earlier in the summer, the complaints seemed to have stopped, and Garvin worried that the scammers had gone dark before he could pin them down. Now they were calling his cell phone.

Following the prompts, Garvin was transferred to a live agent, who asked his age range and if he made at least $60,000 a year. He passed the test and was quickly put on the line with a second live agent—the charmer. "You've won an all-inclusive trip to one of our fabulous resorts," the agent said. "What do you like to do on vacation, Mr. Garvin?"

Garvin played along. "I like to hang out by the pool and have a few cocktails," he said. Garvin did his best to maintain his composure as he sat in his car scribbling and trying to eke out company names and information from the agent. His sister-in-law had long since given up and gone inside.

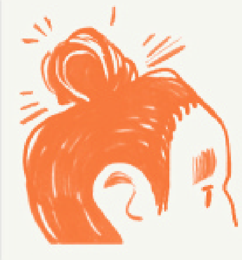
When the agent sensed that the hook was in, he went in for the close: "This trip is valued at $4,000, but today it's only $999. We accept Visa, Mastercard, or American Express. Which card would you like to use today?"

Garvin deflected. "If I make this purchase without asking my wife, I'm in the doghouse," he told the agent. "It's better to ask for forgiveness than permission," the operator replied. Still, he gave Garvin a callback number and other information. When Garvin hung up, he drove home as fast as he could. Armed with new websites and names, he spent all night at his laptop. By the next morning, after sleuthing through social media and Mexican phone databases, he knew the real name of the call center agent and found the Facebook page of the call center's CEO—people he could tie directly to the TripAdvisor scam. Now they had the evidence they needed to bring a full dossier to the FCC.

As Garvin gathered information about call centers in Mexico, Young began sending them cease and desist letters, explaining that TripAdvisor had learned of their ploy and threatening to turn them in to Mexican authorities. Most just ignored him or pleaded ignorance. Finally, one company—seeking to demonstrate its good intentions (or avoid a lawsuit)—offered up a key piece of information. Garvin and Young had assumed that the Mexican call centers were making the robocalls themselves. But they weren't. They paid someone in the US to do that. Best of all, the newly solicitous Mexican company knew the first name and phone number of their American robocaller.

Young contacted Thompson at the FCC again. "Let's have another meeting," he said. With the first name, phone number, and some googling they had found their man: Adrian Abramovich.

Small robocaller
spot illo
to kick off the new
section. (illustrating
the bolded text in the
draft)



PART FOUR

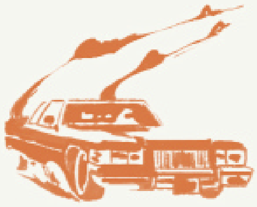
ON APRIL 18, 2018, ADRIAN Abramovich appeared before the US Senate Committee on Commerce, Science and Transportation. Ten months earlier, with help from Garvin and Young, the FCC had accused him of a "massive caller ID spoofing operation" and slapped him with a proposed $120 million fine, then the largest in the history of the FCC. The agency identified Abramovich as the source of 96,758,223 illegal robocalls. The laws governing robocalls are complex and sometimes contradictory, enforced by multiple agencies, and with layers of exceptions and loopholes. But the gist is simple enough: no calling cell phones, no using automated or prerecorded messages, and no using fake names or numbers. According to the FCC, Abramovich had broken all of these rules.

Abramovich arrived at the Russell Senate Office Building looking bewildered, as you might expect of someone compelled by congressional subpoena. In the past few years, there hadn't been much that Democrats and Republicans in Congress could agree on. Health care, immigration, taxes, deficits—every debate, every topic and idea was us vs. them. Here, finally, was an issue that perfectly bridged the partisan divide: a burning hatred of robocalls. As soon as the hearing began, the senators pounced, clearly relishing the chance to lay into the stout man at the witness table. Abramovich, wearing a suit and glasses and with his hair pulled back into a neat man bun, looked trapped.

Senator Richard Blumenthal kicked things off. Abramovich, Blumenthal said, had assembled a "phenomenal record of consumer abuse." Looking directly at him, he declared: "You have become the face of this problem."

Though Abramovich refused to talk about his own actions, he insisted that all of the vacation packages were on the up-and-up and that no consumers were misled. Sure, the calls were actually just the entrée to find customers for expensive time-shares, but it was all there in the fine print of the deals. (The FCC was only interested in the robocalling violations, not whether the trips themselves were scams.) Besides, he was just the middleman, connecting American consumers to Mexican companies. As the questioning continued, Abramovich took great care to distinguish the "good guy" robocallers like himself, who were offering "legitimate services or products," from the true scam artists. "I receive four or five robocalls a day," he added, as if to give his Everyman bona fides. "I never answer the phone." These replies elicited little sympathy from the senators. "The efficiency and the magnitude of your robocall campaign is truly historic," said Senator Ed Markey, who pointed out that he had written the Telephone Consumer Protection Act, one of the laws that Abramovich was accused of violating. "Do you understand why it irritates people? Do you understand why they don't want these unwanted calls, Mr. Abramovich?"

It went on like that: 45 minutes of US senators scolding the seemingly baffled kingpin of robocalling.



PART FIVE

I FOUND ABRAMOVICH THE SAME WAY HE PROBABLY FOUND the people he autodialed: through a public database listing his name, phone number, and home address. He lives in a posh Miami neighborhood in a gated oceanside community with the requisite pool, tennis courts, and security guards. The large stone-and-brick villas are organized around handsome courtyards with palm trees planted in the middle.

I knocked on the door, unannounced. Abramovich answered in a tight Lacoste T-shirt and skinny distressed jeans, and I thrust my hand out before he could shut the door. We stood in the doorway talking for half an hour until Abramovich's wife joined us and invited me in.

Abramovich has a thing for bad guys. His man cave, which doubles as a home office, is decorated with figurines, paintings, and memorabilia depicting infamous movie villains like Scarface, the mobsters from *Goodfellas*, and Freddy Krueger. A record collection lines one wall, and an 80-inch TV is positioned in front of a set of plush black chairs and a black couch. Beside the record collection is his desk. Here it was: the compact headquarters of an alleged robocall empire from which Abramovich was said to place millions of calls a day. Off-the-shelf software can run automatically, moving through lists of phone numbers and other personal data available for purchase. The only limit to a robocall business is the amount of bandwidth you're willing to pay for; the potential number of calls Abramovich could have made was unlimited.

As we toured the house, Abramovich's wife pointed to their collection of South American art, while her husband described his current predicament with a sullen, dejected air, all sighs and slow head shakes. Despite the surroundings, he protested that his work had not made him rich—there was no way he could pay the $120 million fine or even a fraction of it. "I'm on monthly payment plans for everything," he told me. "They're not going to find a boat or five condos anywhere." His wife, while keeping the family's three small dogs at bay, noted, unprompted, that the Ferrari in the garage had been purchased in 2010 and was paid off in installments over five years.

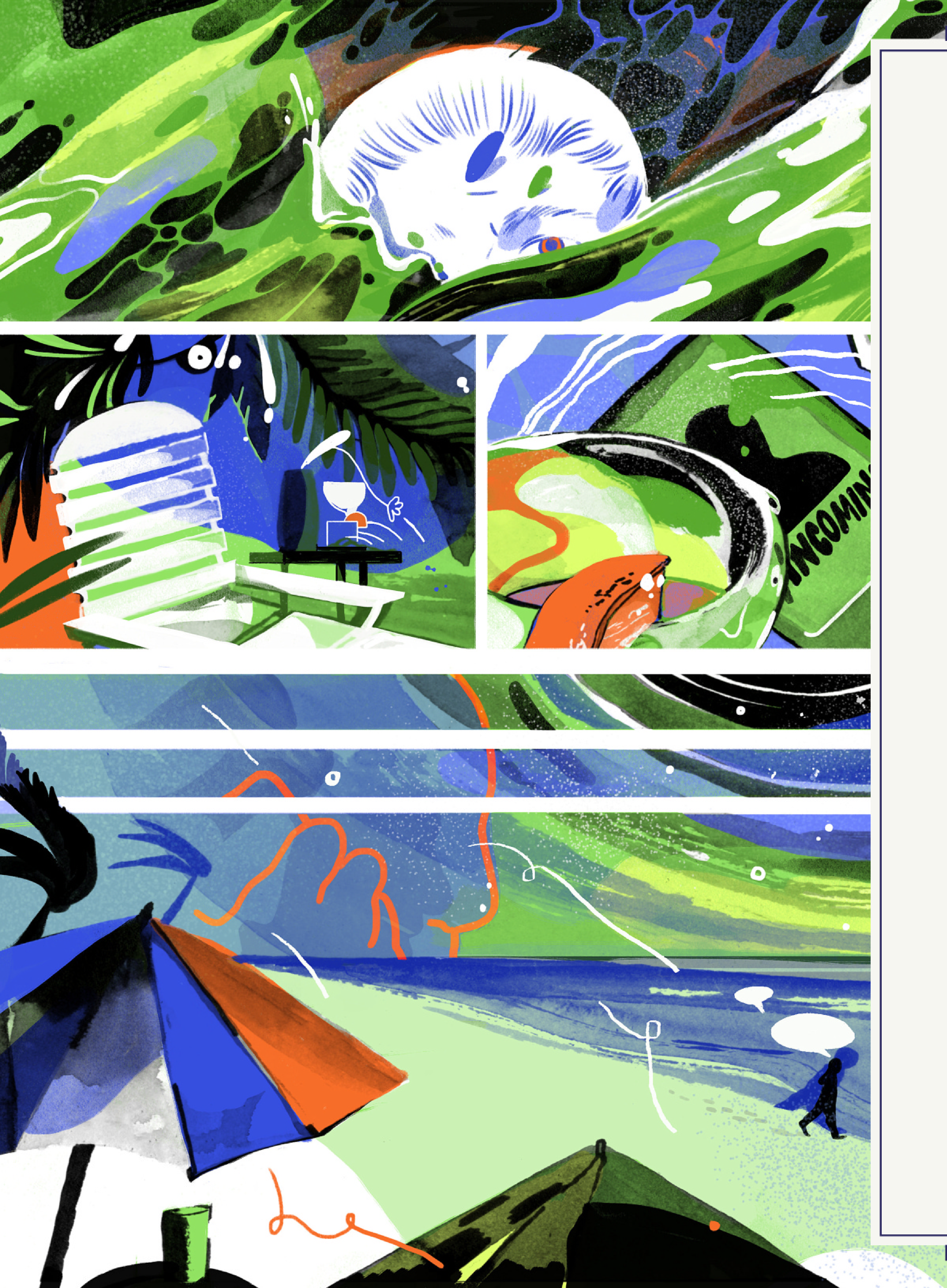
Abramovich talked about a lot of things: Senator John Thune's height (shorter than you'd think from TV), infamous pharma bro Martin Shkreli. ("He was laughing in front of the Senate. I was scared. I was really scared.") But he mostly wanted to vent. After the FCC's citation, his home had been inundated with hate mail and angry phone calls; his bank had closed his account without explanation and refused to let him open a new one. Family members had stopped talking to him.

The humiliating spotlight of national condemnation came as a shock to him. He had immigrated to the US from Argentina—he still speaks with a thick accent—and over the past two decades, he has formed and led at least 12 corporations in Florida, according to the FCC, most of them dedicated to telemarketing and travel deals.

For all those years, calling maybe billions of people, he had been hidden from consumer anger and opprobrium. His prolific telemarketing got him into trouble in 2007 when AT&T Mobility got a consent judgment and injunction against him for unlawful telemarketing, but it wasn't big news. The FCC ordeal was something entirely new and unpleasant.

The worst part, he said, was being served the Senate subpoena. It was Good Friday, and he was at his lawyer's office talking about the case. His youngest daughter, barely a teenager, answered the door before his wife intervened. When a US marshal tried to hand Abramovich's wife the subpoena, she let the papers drop to the ground. "You haven't served me anything," she said. The following Tuesday, three cars came screeching into their home's shared courtyard, sirens blazing, and five marshals came to the door with the subpoena, Abramovich said. The neighbors came out to gawk. (The US Marshals Service said the subpoena was served "in a lawful manner.")

People didn't know his side of the story, Abramovich protested, but they had already decided that he was the bad guy. Abramovich told me that his lawyer had advised him not to talk to anyone, and he wavered as we spoke, alternating between brash defiance and victimhood. The case was now in the hands of the local US attorney, who was responsible for collecting the FCC's judgment. The prosecutor hadn't filed a complaint yet, but Abramovich, who has denied any intent to defraud customers, was planning to defend himself in court and then plead down to a lesser settlement based on his inability to pay the full fine. No matter what amount the settlement reached, though, he still felt wronged. "People don't want to know," he told me. "They don't care." Then he asked me to leave.


INCOMIN

PART SIX

EVEN WITH ABRAMOVICH OUT OF THE GAME, THE number of robocalls continues to explode. Many calls are from big companies doing what's allowed (like dunning their customers), and some are from big companies doing what's not (Dish Network was ordered to pay $280 million in 2017 for making calls to numbers on the Do Not Call Registry). And the netherworld of scammers keeps growing. Shady new kingpins are always popping up, eager to make their fortune. The FCC acknowledges that it is fighting a losing battle. By the end of this year, according to First Orion, a maker of caller ID and call-blocking software, nearly half of all telephone traffic in the US will be spam calls. "Going after a single bad actor is like emptying the ocean with a teaspoon," one FCC commissioner wrote in her opinion commending the fine against Abramovich. "And right now we're all wet."

More than three years on, Garvin is still tracking robocalls. His methods now include fake credit card numbers, burner email addresses, even tricks for inducing a call center operator to text him from a personal number. He still trawls the TripAdvisor forums for complaints. Sometimes the work relates to an ongoing investigation for TripAdvisor; more often, it's just to scratch his own itch.

One of the jobs that Garvin held before TripAdvisor was editing audio for a *SpongeBob SquarePants* videogame. Listening to hours of dialog, he developed a knack for recognizing voices. Garvin thinks he has identified five or six voices that pop up again and again on the robocalls he's listened to—and he's listened to thousands. He has a new idea: What if he could figure out the identities of those people and uncover the marketplace where robocallers find and hire voice actors? Could he nip a campaign in the bud? Better yet, what if, rather than ignoring robocalls, every American answered every call? If enough people pressed through to the call-center agents and toyed with them for hours, the enterprises would be deprived of sales and the robocallers driven into oblivion!

That's a crazy idea. Even Garvin knows it. And it directly contradicts one of the FTC's recommendations to consumers: When you receive a robocall, just hang up; do not engage. But the idea appeals to Garvin's mischievous side, his fondness for turning the tables on scammers. For the time being, he is content finding angry customers, getting as much information from them as he can, and forwarding it all to the FCC for follow-up and prosecution. Recently, he bought four phones for the exclusive purpose of receiving robocalls. They are still ringing.

COLOPHON

Life-changers that helped get this issue out:

"Green Arrow" by Yo La Tengo; Princess Drool; Hokkaido single-dairy soft serve; cheap umbrellas from Old Navy (though one broke after two days in mild showers); Joan Ocean; javelina-patterned wool socks; @AOC; giving up boba; the strip-mall bar near my childhood home where the default is a double in a water glass; Tamiflu; BLTs with peanut butter; extra-thick Croakies; GuitarLessons365 on YouTube; time-out dolls; the end of my neighbor's EDM phase; ice fishing for northern pike; flatbread from the Kebabery; probiotics, peppermint oil, and fiber pills from Costco; my 3-foot-tall, five-flowered amaryllis; Scandia Family Fun Center; a cuddly dog; splicing together a pair of Dr. Scholl's inserts with cute but painful red cowboy boots; the deletion of an energy-wasting space heater and the addition of a brand-new comforter; atmospheric rivers; the return of avocado season; the pressurized ear spray at the urgent care clinic; putting Tajín on everything.

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A STORY ABOUT CRISPR GENE EDITING:

SHE DIED AT 185. SO YOUNG.

— @rafaelalimandro via Instagram

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